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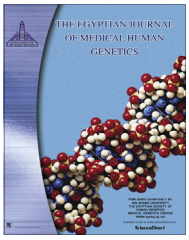

CASE REPORT

Berardinelli–Seip syndrome type 2 – An Egyptian child

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Abstract We report a 2.5 year old male, first in order of birth of first cousin consanguineous parents with the typical features of Berardinelli–Seip congenital lipodystrophy 2 (BSCL2) since birth with moderate mental retardation. He had generalized lipodystrophy with various dermatologic and systemic manifestations. The patient looked older than his age with the loss of buccal pad of fat, hypertrichosis mainly on the back and lower limbs, thick scalp hair, mild prognathism, large hands and feet with prominent joints and muscular hypertrophy. Acanthosis nigricans was evident over the neck and both axillae inspite of the normal level of sugar and insulin. The abdomen was markedly prominent with mild hepatosplenomegaly and enlarged external genitals. Echo-cardiography demonstrated cardiac hypertrophy. Triglyceride level was high with reduced high density lipoproteins (HDL).

1. Introduction

Lipodystrophies represent a heterogeneous group of rare diseases characterized by generalized or partial alterations in body fat development or distribution [1]. Lipodystrophies are most often characterized by selective loss of the adipose tissue from particular anatomical regions, ranging from localized to generalized [1]. Patients with lipodystrophy often have some of the metabolic disturbances such as increased visceral fat, dyslipidemia, and insulin resistance [2]. Lipodystrophies can be classified into "familial" or "genetic" and "acquired" types [3] and can also be a component of certain rare inherited multi-system syndromes [1]. Congenital generalized lipodystrophy (CGL) of the Berardinelli–Seip type (BSCL) is a rare genetic condition characterized by a near total absence of the adipose tissue [4]. Fat cells are present, but are reduced in number and size and contain little fat [5]. It was first described more than a half-century ago by Berardinelli and later by Seip [6]. Patients are characterized by accelerated linear growth, advanced bone age, and marked acanthosis nigricans [4,7]. In addition, umbilical hernia, hepatomegaly secondary to hepatic steatosis that can progress to cirrhosis, splenomegaly, [4,7,8] cardiomyopathy and mental retardation may variably occur [9,10].

There are approximately more than 250 cases of various ethnic origins reported all over the world, with greater frequency in some ethnic groups, mainly in Latin Americans and Arabians [11].

Here we report an Egyptian child with BSCL most probably belonging to type 2 with visceral and dermatologic manifestations in view of its rarity, after taking consent of the parents.

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2. Case report

The case of a 2.5 year old male, first in order of birth of first cousin consanguineous Egyptian parents is reported. The patient was delivered at full term by vaginal delivery after uncomplicated pregnancy. His birth weight was 3 kg. The patient was referred to the Genetics Clinic, Pediatric Hospital, Ain Shams University complaining of unusual facial features.

Since birth the mother noticed that her son was born with empty cheeks. At the age of 6 months, there was a gradual increase in the abdominal size. His parents were normal. His motor development was appropriate for age with mild deficits in mental and communication skills.

On examination, his weight was 14 kg (on 75th percentile), his height was 95 cm (on 90th percentile), and his skull circumference was 47 cm (on 10th percentile). The patient looked older than his age. He had generalized loss of subcutaneous fat, hypertrichosis in the back, thighs and legs, thick scalp hair, low anterior hair line, prominent frontal and supraorbital ridges, loss of buccal fat, decayed teeth, mild prognathism, large low set ears, large hands with tall fingers and clinodactyly of 5th fingers and hypertrophied proximal interphalangeal joints. The feet were large with long toes and the second and the fourth toes overriding the third toe. There was mild hypertrophy of muscles in the calf and the thigh and loss of buttocks fat (Figs. 1–3). He also had thick hyperpigmented patchy areas (acanthosis nigricans) in the neck and both axillae (Fig. 4).

Abdominal examination revealed divarication of recti, protuberant abdomen with the liver spanning 7 cm, non tender, firm in consistency, with sharp border, and smooth surface (Fig. 5). The spleen was 2 cm enlarged along its long axis, firm in consistency and non-tender. Cardiac examination was apparently normal. The back was normal. The genitals demonstrated penile hypertrophy (Fig. 3). Neurologic examination demonstrated normal tone with elicited reflexes.

Lipid profile showed a normal serum cholesterol of 170 mg/dl (N: up to 200 mg/dl), a normal Low-density lipoprotein (LDL) of 102 mg/dl (N: <130 mg/dl) and a reduced HDL 33 mg/dl (N >35 mg/dl) and elevation in triglyceride level 176 (N: 70–160 mg/dl).

Fasting blood sugar was within normal limits 81 mg/dl. (N: 70–110 mg/dl). Liver and kidney functions were also within normal levels.

Abdomino-pelvic ultrasonography revealed mild hepatosplenomegaly and cystitis. ECHO cardiography revealed concentric hypertrophy of interventricular septum

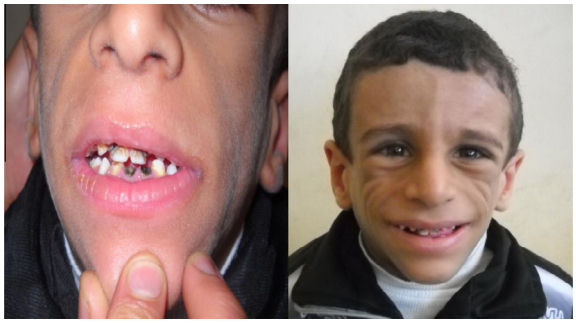

Figure 1 Prominent orbital ridges, loss of buccal fat, decayed teeth and slight prognathism.

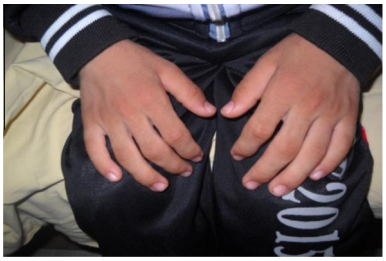

Figure 2 Large hands with enlarged interphalangeal joints.

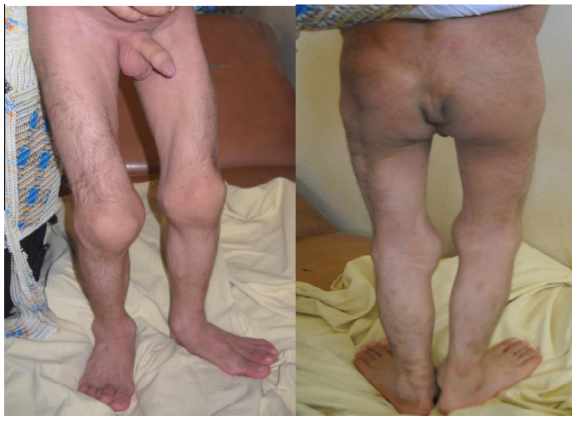

Figure 3 Generalized lipoatrophy, muscular hypertrophy, hypertrichosis, and large joints.

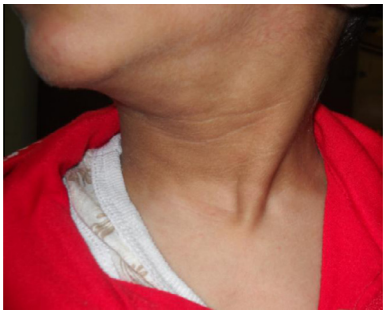

Figure 4 Acanthosis nigricans in the neck.

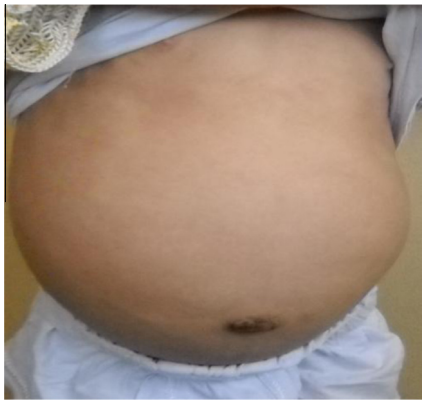

Figure 5 Protuberant abdomen.

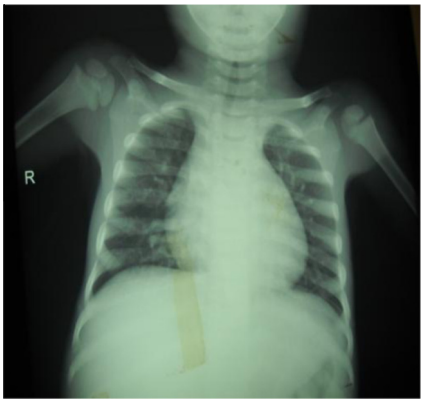

Figure 6 Cardiomegaly in X-ray chest.

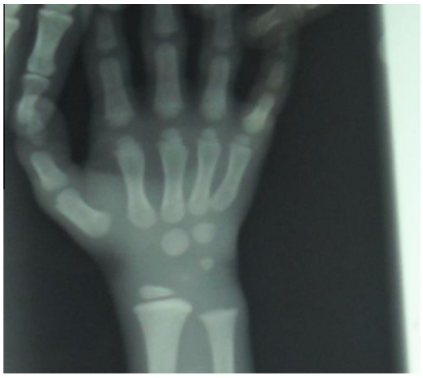

Figure 7 X-ray wrist shows normal bone age.

and left ventricular posterior wall without left ventricular outflow tract obstructions. Chest X-ray revealed cardiomegaly (Fig. 6). X-ray of upper and lower limbs demonstrated normal bones and normal bone age (Figs. 7 and 8). Serum creatine kinase as well as insulin levels were normal. Liver function tests were normal.

3. Discussion

We report a 2.5 year old male patient, with features typical of BSCL. It was suggested that the presence of 3 major or 2 major as well as 2 minor criteria conforms to the diagnosis of BSCL [12].

Major criteria include 1 – Generalized lipoatrophy involving the trunk, limbs and face. 2 – Acromegaloid features with gigantism, prognathism, prominent orbital ridges, enlarged hands and feet, muscular hypertrophy, advanced bone age, clitoromegaly in females and enlarged genitalia in males. 3 – Hepatomegaly. 4 – Elevated serum triglycerides. 5 – Insulin resistance.

Minor criteria include 1 – Hypertrophic cardiomyopathy detected in infancy or later in life. 2 – Psychomotor retardation or mild to moderate intellectual impairment. 3 – Hirsutism with low frontal and posterior hair lines. 4 – Precocious puberty in females. 5 – Bone cysts often diagnosed in the 2nd decade of life.

Our patient had 4 major criteria and 3 minor criteria, so he conforms to the diagnosis of BSCL.

There is a generalized absence of fat due to defects in adipogenesis pathway together with increased destruction of adipocytes as well as inability of adipocytes to store fat [13]. Adipocytes are unable to synthesize and release adipocytokines (leptin and adiponectin), which show decreased levels. Leptin deficiency can lead to decreased metabolic rate, voracious appetite and worsening of metabolic rate. Both leptin and adiponectin deficiency lead to decreased storage of fat in the adipose tissue, deposition of excess fat in liver and muscles, decreased fatty acid oxidation in the skeletal muscles and in the liver, decreased glucose uptake and hepatic gluconeogenesis [14].

The acromegalic appearance of our patient was evidenced by prognathism and enlarged hands, feet, nose and ears. Although growth hormone level was reported to be normal in these patients, insulin like growth factor hypersecretion was found which leads to anabolic processes with rapid skeletal maturation [1]; however our patient had normal bone age.

Our patient had decayed teeth as well as abnormal teeth morphology (triangular) of one central incisor. Dental abnormalities such as talon cusps, moderate and aberrant tooth morphology have been described [15].

Our patient had penile hypertrophy as reported previously in male patients.

Also clitoral hypertrophy was reported to be evident at birth in female patients, but genitomegaly is not apparent after puberty. Reproductive abnormalities are common in female patients. Many have a form of polycystic ovary syndrome.

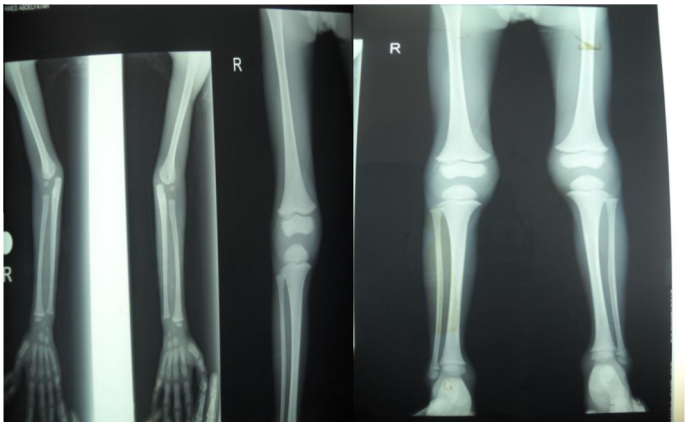

Figure 8 X-ray upper and lower limbs shows normal bones.

Affected men on the other hand have normal reproductive function [16]. Soliman et al. [17] reported a 2 year old Egyptian female with BSCL with pubertal LH and FSH responses to GnRH stimulation. This patient presented with developed breasts, large clitoris and hypertrophied tibia.

Umbilical hernia or prominence seems to be a consistent finding [18]. Our patient had everted umbilicus.

The increased muscle mass or muscular hypertrophy detected in our patient results from storage of glycogen, triglycerides and creatinine accentuated by anabolic processes due to hypermetabolism which characterize these patients [1,4]. Skeletal maturation occurs by the age of 6–8 years. The joints of the hands, and feet may be enlarged [19] as detected in our patient.

Our patient had cardiomegaly and hypertrophic cardiomyopathy as described in other cases [20,21]. This may be due to increased anabolism together with excess energy. Our patient had normal blood pressure; however blood pressure may be slightly elevated in these patients and is not related to cardiac hypertrophy [4,21].

Our patient had normal kidney function although different forms of nephropathy may be associated with lipodystrophy resulting from diabetes mellitus or hyperlipidemia which may be associated with this syndrome [4,18].

Dyslipidemia was observed in our patient with elevated triglyceride level and reduced HDL. This is due to inability of adipocytes to store fat due to abnormal function of glucose transporters with a low level of intracellular glycerol which hampers the storage of triglycerides [13]. Hypertriglyceridemia may result in the appearance of skin xanthomas [4,22] which were not detected in our patient.

Inability to store triglycerides leads to its abnormal deposition with enlarged liver and spleen as detected in our patient which may lead to cirrhosis [4,6]. Also it leads to impaired insulin secretion, insulin resistance and type 2 diabetes [23].

Although our patient had normal blood sugar and insulin levels, he has acanthosis nigricans (AN) which is an early clinical expression of insulin resistance [24]. This indicates that he is starting to get insulin resistance.

In addition to acanthosis nigricans and xanthomas, other dermatologic manifestations such as hirsutism and thick scalp hair were reported previously [5]. Hirsutism of the face, neck, arms and legs may be observed at birth and tends to increase [5]. Our patient had hirsutism on the back and both legs as well as thick scalp hair.

The parents of our patient are first cousins, with no family history of similarly affected persons. However consanguinity is high in Egypt [25] which favors the appearance of autosomal recessive disorders including this syndrome which is reported to be transmitted as an autosomal recessive trait.

Four types of BSCL were described and mutations in 2 genes are responsible for 95% of typical cases [26]. In BSCL1 the AGPAT2 gene located in 9p34 was found to be mutated. This gene encodes the enzyme 1-acylglycerol-3-phosphate acyl transferase 2 responsible for the synthesis of phosphatidic acid from lyophosphatidic acid in the pathway of triacylglycerol synthesis [27]. The 2nd gene found to be mutated is BSCL2 on 11q13 which is associated with BSCL2. This gene encodes seipin protein and is expressed in most human tissues. Individuals with AGPAT2 mutations mostly originate from Sub-Saharan Africa, Maghreb and occasionally from middle eastern countries while those with BSCL2 gene mutation have been described worldwide including whites of varying ethnicities and Middle Eastern Arabs [28]. BSCL1 is a milder variety which presents in the 2nd decade of life and only 10% of patients have intellectual impairments [12,29] in contrast to BSCL2 which presents early in life with a more severe clinical presentation and 80% have mild to moderate intellectual impairments [12]. BSCL3 is caused by mutation in CAV1gene which codes for caveolin protein and is expressed in adipocytes and plays a role in lipid metabolism [30]. Thus in its mutation adipocytes are unable to regulate lipid levels [31–33]. Patients typically have serum creatine kinase (CK) concentrations between 2.5 and 10 times the upper limit of normal in addition to features of classic BSCL with low muscle tone [31]. BSCL4 is caused by mutations in PTRF gene which codes for a protein called polymerase I and transcript release factor which stabilizes and aids in the formation of caveolae. Thus the caveolae are unable to carry out their role in lipid metabolism. BSCL4 presents with generalized lipodystrophy, distal myopathy, muscular hypertrophy, insulin resistance and elevated CK levels [33].

So based on the origin and clinical profile our patient most probably belongs to type 2 as he clinically presents at birth with typical features with moderate mental retardation and normal CK.

To conclude: SCGL2 is a multisystemic and progressive disease. Follow up of patients is important as diabetes mellitus usually develops in teenage years and is insulin resistant. Also early onset of liver cirrhosis may occur with significant morbidity and mentality. In addition hypertrophic cardiomyopathy and diabetic renal failure are potentially lethal complications. So early diagnosis and diet control can bring about a favorable outcome.

References

[1] Carg A. Acquired and inherited lipodystrophies. N Engl J Med 2004;350(12):1220–34.
[2] Hegele RA. Monogenic forms of insulin resistance: apertures that expose the common metabolic syndrome. Trends Endocrinol Metab 2003;14(8):371–7.
[3] Hegele RA. Phenomics, lipodystrophy, and the metabolic syndrome. Trends Cardiovasc Med 2004;14(4):133–7.
[4] Seip M, Trygstad O. Generalized lipodystrophy, congenital and acquired (lipoatrophy). Acta Paediatr Suppl 1996;413:2–28.
[5] Janniger CK, Jager C, Yan AC, Wells MJ, et al. Medscape, Drugs, Diseases & Procedures. Updated April 2, 2014.
[6] Berardinelli W. An undiagnosed endocrinometabolic syndrome: report of two cases. J Clin Endocrinol Metab 1954;14(2):193–204.
[7] Westvik J. Radiological features in generalized lipodystrophy. Acta Paediatr Suppl 1996;413:44–51.
[8] Fleckenstein JL, Garg A, Bonte FJ, Vuitch MF, Peshock RM. The skeleton in congenital, generalized lipodystrophy: evaluation using whole-body radiographic surveys, magnetic resonance imaging and technetium-99m bone scintigraphy. Skeletal Radiol 1992;21:381–6.
[9] Agarwal AK, Simha V, Oral EA, Moran SA, Gorden P, O'Rahilly S, et al. Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. J Clin Endocrinol Metab 2003;88(10):4840–7.
[10] Bhayana S, Siu VM, Joubert GI, Clarson CL, Cao H, Hegele RA. Cardiomyopathy in congenital complete lipodystrophy. Clin Genet 2002;61(4):283–7.

[11] Daher E, Silva Júnior G, Benevides V, Mendonça P, Bezerra H, Silva A, et al. Berardinelli syndrome. A case report with fatal outcome. Invest Clin 2008;49:251–5.
[12] Van Maldergem L. Berardinelli–Seip Congenital Lipodystrophy. 2003 Sep 8 [Updated 2012 Jun 28]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK1212/>.
[13] Figueiredo Filho PP et al. Congenital generalized lipodystrophy. J Pediatr (Rio J) 2004;80(4):333–6.
[14] Farooqi IS, Wangenstean T, Collins S, Kimber W, et al. Clinical and molecular spectrum of congenital deficiency of the leptin receptor. N Engl J Med 2007;356(3):237–47.
[15] Solanki M, Patil SS, Baweja DK, Noorani H, et al. Talon cusps, macrodontia, and aberrant tooth morphology in Berardinelli–Seip syndrome. Oral Surg Oral Pathol Oral Radiol Endod 2008;105(1): e 41–47.
[16] Agarwal AK, Garg A. Genetic basis of lipodystrophies and management of metabolic complications. Annu Rev Med 2006;57: 297–311.
[17] Soliman AT, El-Nawawy AA, El-Azzoni OO, et al. Seip–Berardinelli Lipodystrophy: report of three cases and their endocrine functions. Ann Saudi Med 1995;15(5):501–5.
[18] Garg A. Lipodystrophies. Am J Med 2000;108:143–52.
[19] Dermasdt GL, Sidbury R. The skin. In: Behrman RE, Kliegman RM, Jenson HB, editors. Nelson Textbook of Pediatrics. Philadelphia: W.B. Sounders; 2003. p. 2153–250.
[20] Bjornstad PG, Semb BKH, Trygstad O, Seip M. Echocardiographic assessment of cardiac function and morphology in patients with generalised lipodystrophy. Eur J Pediatr 1985;144: 355–9.
[21] Bjornstad PG, Foerster A, Ìhlen H. Cardiac findings in generalized lipodystrophy. Acta Paediatr Suppl 1996;413:39–43.
[22] Garg A. A gene for congenital generalized lipodystrophy maps to human chromosome 9q34. J Clin Endocrinol Metab 1999;84: 3390–4.
[23] Oral EA. Medscape. Generalized Lipodystrophy. Updated: Mar 10, 2014. <http://emedicine.medscape.com/article/128355-overview>.
[24] Van Maldergem L. Berardinelli–Seip congenital lipodystrophy. Orphanet encyclopedia November 2001. <http://www.orpha.net/data/patho/GB/uk-berad.pdf>.
[25] Shawky RM, El-Awady YM, Elsayed SM, Hamadan GE. Consanguineous matings among Egyptian population. Egypt J Med Hum Genet 2011;12(2):157–63.
[26] Boutet E, El Mourabit H, Prot M, Nemani M, Khallouf E, Colard O, et al. Seipin deficiency alters fatty acid delta9 desaturation and lipid droplet formation in Berardinelli–Seip congenital lipodystrophy. Biochimie 2009;91:796–803.
[27] Agarwal AK, Arioglu E, De Almeida S, Akkoc N, Taylor SI, Bowcock AM, et al. Nat Genet 2002;31:21–3.
[28] Van Maldergem L, Magre J, Khallouf TE, Gedde-Dahl T, Delepine M, Trygstad O, et al. Genotype–phenotype relationships in Berardinelli–Seip congenital lipodystrophy. J Med Genet 2002;39:722–33.
[29] Metwalley KA, Farghaly HS. Berardinelli–Seip syndrome type 1 in an Egyptian child. Indian J Human Genet 2014;20(1):75–8.
[30] Parton RG, Simsons K. The multiple facies of Caveolae. Nat Rev Mol Cell Biol 2007;8(3):185–94.
[31] Kim CA, Delépine M, Boutet E, El Mourabit H, Le Lay S, Meier M, et al. Association of a homozygous nonsense caveolin-1 mutation with Berardinelli–Seip congenital lipodystrophy. J Clin Endocrinol Metab 2008;93:1129–34.
[32] Simha V, Zerwekh JE, Sakhaee K, Garg A. Effect of subcutaneous leptin replacement therapy on bone metabolism in patients with generalized lipodystrophy. J Clin Endocrinol Metab 2002; 87:4942–5.
[33] Hayashi YK, Matsuda C, Ogawa M, Goto K, Tominaga K, Mitsuhashi S, et al. Human PTFR mutations cause secondary deficiency of caveolins resulting in muscular dystrophy with generalized lipodystrophy. J Clin Invest 2009;119:2623–33.