Berardinilli - Seip Congenital Generalized Lipodystrophy
A Case Report

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Abstract

Berardinilli - Seip congenital generalized lipodystrophy (BSCL) is a very rare autosomal recessive disease characterized by near absence of adipose tissue in the subcutaneous region since birth or early infancy and severe insulin resistance. Nearly 120 cases had been reported in the literature. Clinically it showed marked atrophy of subcutaneous fatty tissues, generalized muscle hypertrophy, developmental and learning disabilities in a majority of cases, with acromegaly, coarse facies, enlarged hands, feet and prominent mandible, increased sweating. Hepatomegaly from fatty liver is almost universal and may ultimately lead to cirrhosis. Females present with an enlarged clitoris (clitoromegaly), hirsutism, absence and irregular menses and polycystic ovary and only a few affected women have had successful pregnancies .All cases present with hypertriglyceridemia. Treatment consists of low fat diet and handling of insulin resistance and diabetes.

A 19 months old Arabic female child, resident in Balad-Salahuddin province, was referred to outpatient clinic in Balad general hospital for her unusual facial features. She was a product of uneventful vaginal delivery with a smooth postnatal period. At 3rd month of life, the family noticed unusual gross facies which became more obvious with age.

Key words: Berardinilli- Seip, congenital lipodystrophy, BSCL.

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Introduction

Berardinilli Seip congenital generalized lipodystrophy (BSCL) is named after Berardinilli, who reported the first affected individual from Brazil in 1954 [1]. It is a rare condition characterized by lack of fatty (adipose) tissue in the body. This means that fats must be stored elsewhere, such as in the liver, muscles which leads to serious medical problems. This condition is part of a group of related disorders known as Lipodystrophies which are all characterized by problems with adipose tissue [2].

Mutations in the AGPAT2 and BSCL2 genes cause the two types of disease respectively. The proteins produced from the AGPAT 2 and BSCL 2 genes play an important role in adipocytes which are the fat- storing cells in adipose tissue, so mutation of these genes will lead to disruption of normal development and function of adipocyte [3, 4].

Clinical manifestations

In B.S.C.L. patients are clinically apparent from birth or early infancy. Common features include high level of fats (triglycerides) in the blood stream (hypertriglyceridemia). It also causes an abnormal build up of fats in the liver (hepatic steatosis), which can damage this organ. An accumulation of fats in the heart can cause heart disease (Hypertrophic Obstructive Cardiomyopathy HOCM), which can lead to heart failure and sudden death [3]. Hepatomegally secondary

to hepatic steatosis, and skeletal muscle hypertrophy occurs in all aff ected individuals H.O.C.M. is reported in 20%-25% of affected individuals and is a significant cause of morbidity from cardiac failure and early mortality [3].

Peoples with Berardinilli-Seip congenital lipodystrophy have a distinctive appearance, the combination of an almost total absence of adipose tissue and overgrowth of muscles tissues makes these individuals appear very muscular, they also tend to have a large chin, prominent bones above the eyes (orbital ridges), and large hands and feet [2]. Affected female may have an enlarged clitoris (clitoromegaly) and males also tend to have enlarged genitalia [2, 5].

Affected individuals develop insulin resistance and approximately 25%-35% develop Diabetes mellitus between ages 15-20 years. Berardenilli-Seip congenital lipodystrophy is usually diagnosed at birth or soon thereafter [3].

Three major criteria plus 2 or more minor criteria make the diagnosis of B.S.C.L. very likely [3, 7]. Major and minor criteria are summarized in table (1).

Table (1): Major and minor criteria of Berardinilli Seip congenital generalized lipodystrophy.

Lipoatrophy affecting the trunk, limbs, and face. It appear since birth or during the first months of life , this give an athletic appearance. Acromegaloid features include gigantism, muscular hypertrophy, advanced bone age, prognathism , prominent orbital ridges, enlarged hands and feet , clitoromegaly and enlarged external genitalia in male. • Hepatomegaly, secondary to fatty liver in early life and to cirrhosis, late in the disease course. Elevated serum concentration of triglyceride, elevated S.TG up to 80 gm/ l and is sometimes associated with hypercholesterolemia. • Insulin resistance .Increase serum concentration of Insulin and C - peptide may occur starting in the first years of life. Overt Diabetes mellitus usually develops during the second decade.	• Hypertrophic cardiomyopathy, may present in infancy or develops later on. • Psychomotor retardation which is mild (Intelligence quotient 50-70%) to moderate (IQ 35-50%) intellectual impairment. • Hirsutism manifested by low frontal and posterior hair line, hypertrichosis is apparently independent of hormonal stimulation. • precocious puberty. In females in a series of 75 individuals with BSCL. 3 females underwent puberty before 7 years (Van maldergem *et al* 2002). • Bone cysts, occur in (8%-20%) of cases located in in the epiphysis and metaphysis of long bones, its often diagnosed during second decade. • phlebomegaly; prominence of the veins of the upper and lower limbs is observed; in part due to lack of subcutaneous fat [3].

Differential diagnosis

Congenital generalized lipodystrophy (C.G.L.D.), individual in this condition typically have S. creatinine Kinase concentration between (2.5-10) times upper limit of normal, in addition to features resembling B.S.C.L. Other differential diagnosis in infant include Short syndrome which is characterized by short stature, but slit lamp examination of the eyes easily differentiate it from BSCL. Progeria syndrome can be differentiated from B.S.C.L. by prominent veins on scalp, premature teething and pseudohydrocephaly. Neurometabolic lysosomal storage disease; Gauchers disease type 2, Krabbe disease. Childhood Dunningan lipodystrophy can mimic BSCL but here face is spared. Rabson Mendenhall syndrome presented with pure insulin resistance [6].

Other differentials diagnosis include neonatal progeria and Russell-Silver syndrome [7].

Management

The following clinical evaluations are recorded; assessment of pubertal status according to Tanner chart, neurological examination, search for signs of liver and muscles dysfunction, search for evidence of H.O.C.M. and possible orthopedic problems (reduced hip mobility, genu valgum.

Complete ophthalmological examination including slit lamp examination, testing of cognitive ability with age appropriate scales.

The following laboratory investigations should be done to confirm or rule out the disease; complete blood count, serum creatinine phosphokinase, serum electrolytes, aspartate transaminase, alanine transaminase, blood urea, serum creatinine, insulin level and C peptide, Serum triglyceride and cholesterol level, serum protein and electrophoresis and oral glucose tolerance test. If possible growth hormone level, Immunoglubulin G, M, A, E, C3 level, CH50, C3' C4 apolipoprotien. Echocardiography, and Liver function test. Skeletal survey especially long bones for bone cyst and bone age maturation.

Restriction of fat intake to be 20-30% of total dietary intake sufficient to maintain normal triglyceride serum concentration. Fabric acid derivatives and n-3 pufa derived from fish oil can be tried. Special education is required for individuals with psychomotor and intellectual disabilities.

The Case report

We reported a case of B.S.C.L. which up to our knowledge is the first Iraqi child reported with this disease, the earlier case to this one was from Saudi Arabia.

A 19 months old Arabic female child, resident in Balad-Salahuddin province, was referred to outpatient clinic in Balad general hospital for her unusual facial features. She was a product of uneventful vaginal delivery with a smooth postnatal period. At 3rd month of life, the family noticed unusual gross facies which became more obvious with age. Permission to conduct this study was obtained from hospital and family of female child was also informed that they have full right to discontinue or refuse to participate in this study.

The parents are 1st degree cousins and have no other children. There is no family history of similar condition.

On examination she had a generalized lipoatrophy with no fat noticed or felt over the buttock, face, shoulders & limbs. She had coarse features, low anterior hair line, empty checks, prominent orbital ridges, large ears, figure (1). There was obvious muscular hypertrophy particularly in the thigh, shoulder, figure (2), hepatomegaly 3cm below costal margin, it was soft and non-tender.

Figure (1): Showing coarse (acromegaloid) facies of the child

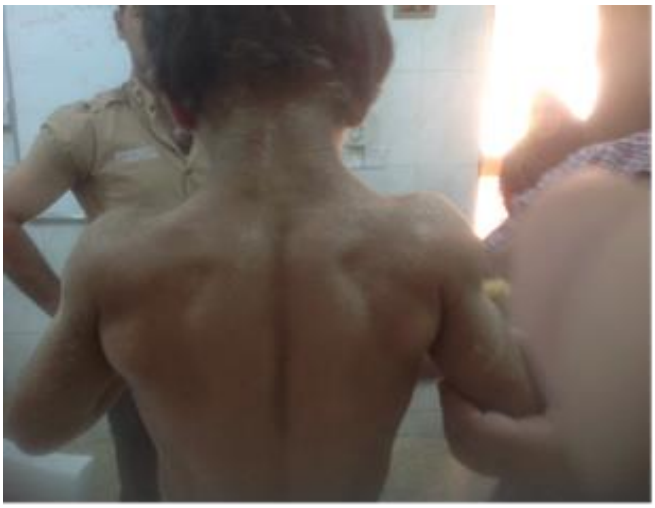

Figure (2): Showing muscular hypertrophy of back and shoulders

The hand and feet were long with prominent veins over arms and shoulders (phlebomegaly), figure (3). She also had clitoromegaly, figure (4). The length was higher than her target length for age. The growth parameters (length, weight, head circumference) were 89cm (above 97th centile), 15kg (on 75th centile), 48.6 cm (below 90th centiles) respectively. Formal developmental assessment (Denver developmental screening test) showed moderate delay in speech and social skills with mild to moderate delay in fine motor skills, whereas gross motor was maintained

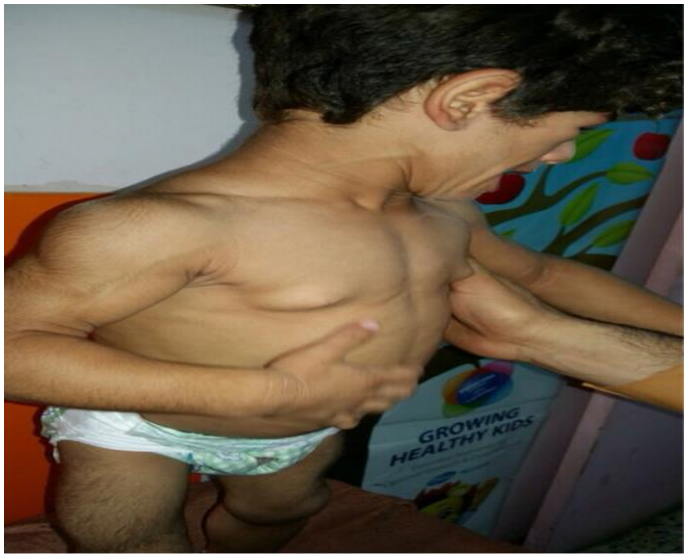

Figure (3): Showing phlebomegaly (dilated viens) and hirsutism (mainly in lower limbs)

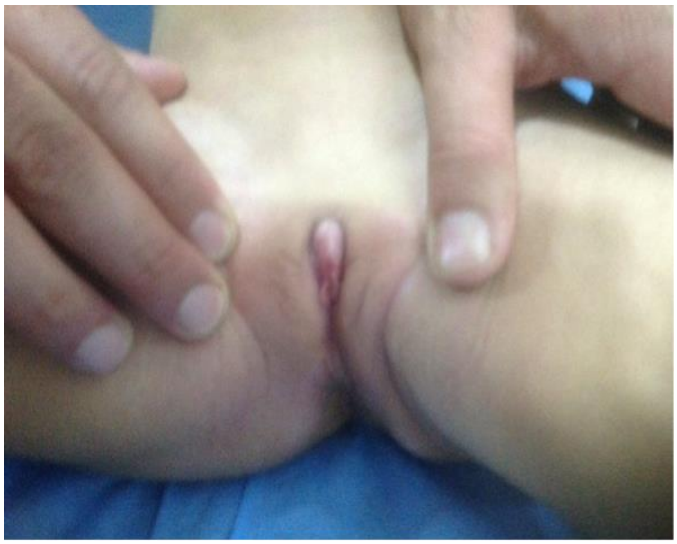

Figure (4): Showing clitoromegaly

The results of biochemical tests and radiological tests are shown in table (2). These showed high triglyceride (TG) level in female case report.

Table (2): Results of biochemical and radiological investigations

No.	Test	Result
1	Complete blood count	Normal
2	Fasting blood sugar	4.3 mmol/l
3	Serum cholesterol	4.1mmol/l (3.2-6.2 mmol/l)
4	Serum triglycerides	3.1 mmol/l (0.9-2.4 mmol/l)
5	Liver function test and renal function test	Normal
6	Total serum protein and albumin/ globulin ratio	Normal
7	Thyroid function test	normal
8	CPK (serum creatinine phosphokinase)	Normal
9	Serum 17 OH progesterone	75 ng/dl (less than 100 ng/dl)
10	Growth hormone level	7.5ng/ml (less than 20ng/ml)
11	Immunoglobulin profile	IgG 1.75mg/dl (313-1.170mg/dl) IgA 51mg/dl (36-79mg/dl) IgM 102 mg/dl (46-152mg/dl)
12	Skeletal survey and bone age	Advanced bone age (bone age of three years old)
13	Chest x-ray , ECG	Normal
14	Echocardiography	Normal
15	EMG and NCV	Normal distal motor latencies, normal CMPA amplitude , normal needle EMG

Discussion

The diagnosis of this case as BSCL have been made confidently from the typical dysmorphology, the findings on clinical examination and the blood biochemistry [6]. Presence of 3 established major criteria plus 2 or more minor criteria establishes the diagnosis.[3].

The child has 4 of the 5 previously listed major criteria, lipoatrophy, acromegaloid features, hepatomegaly, and elevated serum triglyceride, in addition to 4 minor criteria including hirsutism, plebomegaly, precocious puberty and psychomotor retardation.

The acromegaloid features in this child such as prognathism and long hands and feet can be attributed to insulin-like growth factor [IGF] hyper-secretion leading to anabolic processes with a rapid skeletal maturation (advanced bone age). The generalized muscular hypertrophy, thereby giving the child an athletic appearance is due to storage of abundant muscle glycogen and triglycerides accentuated by the anabolic processes due to hypermetabolism is an important characteristic of BSCL.[1,7] Hepatomegaly is the result of the anabolic processes operative in BSCL, further complicated by hepatic steatosis. Our child had already developed hepatomegaly without evidence of cirrhosis (absence of jaundice and stigmata of chronic liver disease, normal liver function test) .

Investigations like CPK, 17 OH progesterone, GH level, Thyroid function tests, EMG and NCV were done to exclude other differential diagnosis

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