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Abstract

Congenital generalized lipodystrophies (CGLs) are very rare autosomal recessive disorders which have four types. Of the four CGL types, BSCL2 (Berardinelli–Seip Congenital lipodystrophy type 2) is the result of mutations in the BSCL2/seipin gene. BSCL2 that is the most severe lipodystrophic phenotype is characterized by generalized lipodystrophy, overgrowth, acanthosis nigricans, hepatomegaly, insulin resistance, and hyper-triglyceridemia. BSCL2 gene is responsible for encoding a protein called seipin. Seipin is responsible for production and accumulation of lipid droplets in the endoplasmic reticulum membranes and their storage inside the cells. Mutation in this gene disrupts this protein. The result is deficiency of lipid formation in the endoplasmic reticulum which causes CGL2 or BSCL2. We report a 4-year-old Iranian girl with typical findings of BSCL2. Molecular analysis of BSCL2 and BSCL1 genes by the sequencing method showed a novel homozygous mutation in the BSCL2 gene.

Keywords: Congenital Generalized Lipodystrophy; Berardinelli-Seip Lipodystrophy; BSCL2 Gene; Seipin; Iranian Novel Mutation.

Introduction

CGL (Congenital generalized lipodystrophy) is a rare genetic disease characterized by near complete loss of the adipose tissue along with increased abnormal fat accumulation in other organs including the liver and muscles. Inherited lipodystrophies are genetically inherited from carrier parents and arise from the specific gene mutations. Inherited lipodystrophies include BSCL (Berardinelli–Seip congenital lipodystrophy) type 1–4 (1). Each BSCL type is known by mutations in one of the four genes. These genes are AGPAT2 (BSCL1), Seipin (BSCL2), CAV1 (BSCL3) and PTRF (polymerase I and transcript release factor)/Cavin (BSCL4) (2). CGL type 1 (CGL1, OMIM 608954) and type 2 (CGL2, OMIM 269700) which are also known as Berardinelli-Seip congenital lipodystrophy types 1 and 2, represent near absence of the body fat at birth or in early infancy with severe insulin resistance leading to diabetes mellitus, hypertriglyceridemia, and hepatic steatosis. In addition to hepatomegaly and generalized muscular hypertrophy, patients have acromegaloid features such as enlarged hands and feet, acanthosis nigricans, and excessive body hair. A significant number of patients develop hypertrophic cardiomyopathy (3). BSCL
was first reported by Berardinelli (1954) in Brazil (4), and then by Seip (1996) in Norway (5). In the European literature, the terms Seip syndrome, generalized lipodystrophy, and congenital generalized lipodystrophy (total lipodystrophy) have been used in different studies (6). This disease is very rare in the United States where the prevalence is reported as one in 10,000,000 population (7). The occurrence of this disease is quite different in other ethnic groups. For example, its prevalence is one in 500,000 in Portugal, and one in 200,000 in Lebanon (6-7).

Berardinelli-Seip congenital lipodystrophy type 1 and 2 are known to be associated with these genes: AGPAT2 is associated with BSCL1(8-9) and BSCL2 gene associated with BSCL type 2 (1). BSCL2 gene is mapped to chromosome 11q13, and AGPAT2 to chromosome 9q34.3. Mutations in BSCL2 causes CGL2. The gene product of BSCL2 is a protein named seipin, which has an unknown function. Therefore, how BSCL2 mutations cause CGL remains to be understood. There is evidence that seipin is strongly involved in the production and development of lipid droplets in the endoplasmic reticulum (ER) of the cells. It should be noted that patients with seipin mutations have a higher prevalence of mild mental retardation and hypertrophic cardiomyopathy than those with CGL1 (1, 8, 10). The Seipin/BSCL2 gene was at first recognized as a loss-of-function gene for congenital generalized lipodystrophy type 2 (CGL2). There are other gain-of-function mutations in this gene, mostly mis-sense mutations, that cause different autosomal dominant neurodegenerative disorders such as Silver syndrome/spastic paraplegia 17 (SPG17), distal hereditary motor neuropathy type V and some variants of Charcot-Marie-Tooth disease type 2. Because of these variable phenotypes, Ito and Suzuki (2009) proposed that seipin-related motor neuron diseases should be collectively referred to as seipinopathies (11). In this study, we report a 4-year-old Iranian affected girl with typical symptoms of Berardinelli-Seip congenital lipodystrophy and a novel mutation in the BSCL2 gene.

Material and Methods
Study Subject:
A 4-years-old girl was referred to the genetic counseling center of Hormozgan Province Welfare Organization for diagnosis of a very unusual illness. The proband was the second child of a first cousin couple. Her parents and older brother were healthy. She was born after an uneventful pregnancy through normal vaginal delivery. Measurements at birth were all within normal limits. She was the only affected case in the pedigree (Figure1). On physical examination, her height was 112 cm, which is in 97th percentile of the National Center for Health Statistic (NCHS) growth chart, and weighed 17 kg, which is between the 50th and 85th percentiles of the NCHS growth chart. Clinical findings were neuro-developmental and speech delay, mild to moderate mental retardation, athletic musculature, generalized lipoatrophy, progeroid face, curly hair, acanthosis nigricans in the groin and axillary area, bilateral gynecomastia, massive hepatomegaly and umbilical hernia (Figure 2). Laboratory tests showed hyper-triglyceridemia (340 mg/dL) and elevated serum glutamic oxaloacetic transaminase (SGOT) (52), serum glutamic pyruvic transaminase (SGPT) (63) and alkaline phosphatase (1420). Fasting blood sugar (FBS) was 89 mg/dL. Thyroid function tests, low density lipoprotein (LDL), high density lipoprotein (HDL), and cholesterol levels were in the normal range. Histological examination of the liver biopsy specimen showed extensive fatty change and steatosis.

According to the clinical findings, the impression was Berardinelli-Seip generalized lipoatrophy (CGL2). After obtaining informed consent from the family, we obtained a blood sample in an EDTA containing tube and the genomic DNA was extracted using the standard protocol. All exons and exon-intron boundaries of BSCL2 and BSCL1 were sequenced.
Results:
Different exons and splice junctions of Bscl2 and Bscl1 genes were sequenced. A novel homozygous mutation in the BSCL2 gene was detected. The result was c.150_212+28del, insGAA. It means that 91 bases were deleted and three nucleotides (GAA) were inserted into the deleted area. The final result was deletion of 3’ end of exon 2 and the consensus sequence of intron 2. It was a deletion-insertion abnormality that has not been reported before. BSCL1 gene analysis was normal.

Discussion:
Berardinelli-Seip Congenital Lipodystrophy (BSCL) is a rare disorder worldwide which was first reported in Brazil in 1954 (4). It is characterized by near total absence of the adipose tissue since birth (5, 6). Besides Brazil, family clusters have been reported in Europe, Lebanon, Turkey, Oman, and other ethnic groups (5).

Three major criteria or two major plus two or more minor criteria make the diagnosis of BSCL very easy. The major criteria are: 1) lipoatrophy affecting the trunk, limbs, and face, 2) acromegaloid features, 3) hepatomegaly, 4) elevated serum concentrations of triglycerides, 5) insulin resistance, 6) elevated serum concentrations of insulin and C-peptide, overt clinical diabetes mellitus usually develops during the second decade, and 7) acanthosis nigricans of the groin, neck, and axillae sometimes with a verrucous appearance.

The minor criteria are: 1) hypertrophic cardiomyopathy, 2) psychomotor retardation or mild to moderate cognitive impairment, 3) hirsutism and hypertrichosis, 4) precocious puberty in females, and 5) phlebomegaly (6, 9). Our patient showed at least 5 major criteria which were lipoatrophy, acromegaloid features, hepatomegaly, hypertriglyceridemia and
acanthosis nigricans of axillae. Our Case also showed 4 minor criteria which were psychomotor retardation, hypertrichosis, precocious puberty, and phlebomegaly. Thus, according to the mentioned criteria, this case was typical for a diagnosis of CGL2 or BSCL2. Furthermore, to our knowledge, this case is the first CGL2 type disease reported in Iran. Bozorgmehr et al. (2009) reported an Iranian case but its type was not identified (12). Another case of BSCL1 was reported by Rostami et al. (2013) in Iran; they identified a mutation in the AGPAT2 gene in the 7-year-old affected girl (13). Using a genome-wide linkage analysis, Garg et al. (1999) found evidence of linkage of BSCL1 with the locus 9q34 (9). Furthermore, Magré et al. (2001) identified another disease locus, BSCL2, on chromosome 11q13(1). Mutations in the seipin gene were identified in families from Lebanon, Turkey, India, South Africa, Brazil, and Europe. Rajab et al. (2002) found a mutation in the BSCL2 gene in a group of Omani patients (14).

A number of diseases should be considered in the differential diagnosis of BSCL2: in infancy: neonatal progeroid syndrome, neurometabolic lysosomal storage disorder such as Gaucher type 2, Krabbe disease, Russell diencephalic syndrome, and leprechaunism or Donohue syndrome; in childhood: familial partial Dunnigan–Koëberling lipodystrophy, insulin-dependent diabetes mellitus, acquired generalized lipodystrophy (Lawrence syndrome), and Hutchinson-Gilford progeria syndrome; in adulthood: acquired partial lipodystrophy (Barraquer-Simons syndrome), lipodystrophy associated with human immunodeficiency virus infection (AIDS), partial lipodystrophy with C3 nephritic factor and acquired generalized lipodystrophy (Lawrence syndrome) (15). According to the patients phenotype, these differential diagnoses were not considered as the final diagnosis.

In conclusion, in this study, we reported a 4-year-old girl with typical clinical features of Berardinelli-Seip syndrome type 2 (BSCL2). Molecular analysis was used for the diagnosis of this genetic disease. We found a novel mutation in this patient which was not previously reported in the literature.

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References