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Clinical case

AGPAT2 gene mutation in a child with Berardinelli-Seip congenital lipodystrophy syndrome

Mutation du gène AGPAT2 chez un patient avec un syndrome de lipodystrophie congénitale de Berardinelli-Seip

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Abstract

Berardinelli-Seip congenital lipodystrophy (BSCL) syndrome is an autosomal recessive disorder, caused by mutation in the *AGPAT2* gene, which could lead to insulin resistance and variety of complications. Herein, a 7-year old girl is presented with generalized loss of subcutaneous fat, prominent pectoral and thigh muscles and an early telarche. Laboratory studies revealed an elevated level of serum triglyceride. Ultrasonograph demonstrated enhanced size of ovary containing multiple mature follicles. Considering the clinical phenotype, *AGPAT2* gene was sequenced which showed homozygote c.514G > A mutation. Therefore, the diagnosis of BSCL was confirmed in this patient.

Résumé

Le syndrome de lipodystrophie congénitale de Berardinelli-Seip est une maladie héréditaire autosomale récessive dont la cause est une mutation du gène *AGPAT2*, ce qui augmente la susceptibilité à la résistance à l'insuline et à plusieurs complications. Nous rapportons le cas d'une fillette de sept ans présentant une perte généralisée de graisse sous-cutanée, une proéminence des muscles pectoraux et de la cuisse et une télarche précoce. La biologie montrait un taux élevé des triglycérides plasmatiques. L'échographie a mis en évidence une augmentation de la taille des ovaires avec présence de multiples follicules matures. Devant ce phénotype clinique, le gène *AGPAT2* était séquencé et montrait une mutation homozygote c.514G > A, confirmant le diagnostic de lipodystrophie de Berardinelli-Seip.

1. Introduction

Lipodystrophic syndromes are characterized by lipoatrophy or fat loss, which may be acquired or possess a genetic basis [1]. The extent and severity of the fat loss differs; it may be small and localized, limited to the limbs (partial) and generalized which affects the whole body fat [2]. The scope of the lipoatrophy correlates with the severity of symptoms and complications [1,3]. The last two types predispose the patient to insulin resistance and its complications, including diabetes mellitus, hypertriglyceridemia, hepatomegaly and hepatic steatosis, acromegaloid features, bone cysts and acanthosis nigricans [2,4,5].

Berardinelli-Seip congenital lipodystrophy (BSCL, OMIM# 608594) syndrome, also known as congenital generalized lipodystrophy (CGL), is an autosomal recessive disorder, caused by mutation in the 1-acylglycerol-3-phosphate O-acyltransferase 2 (*AGPAT2*, OMIM*603100) gene [2]. AGPAT2, mostly expressed in adipose tissue, is a critical enzyme involved in converting glycerol-3-phosphate to triglycerides and phospholipids and lysophosphatidic acid to phosphatidic acid. It also

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plays a role in acylation of fatty acids at the glycerol moiety [2]. Therefore, its deficiency leads to lower production of triglyceride and [6].

Herein, a patient with generalized loss of subcutaneous fat, prominent pectoral and thigh muscles and an early telarche is presented in whom mutation in the *AGPAT2* gene was detected. To our best knowledge, this is the first report of BSCL syndrome from the country.

2. Case report

A 7-year-old girl was referred to the Children's Medical Center Hospital, the Pediatrics Center of Excellence in Iran, with generalized loss of subcutaneous fat and bilateral telarche. Her mother was 24 and her father was 32 and they were second-degree cousins. There is no positive family history for a similar condition. She was term at birth and was born through vaginal delivery followed by an uneventful postnatal period. Prominent pectoral and thigh muscles, prominent subcutaneous veins, and enlargement of toe, mandible and finger joints were detected.

Her height was 114 cm which is 50th percentile of the national center for health statistic (NCHS) growth chart and weighed 22 kg equaling 50th percentile of the NCHS growth chart and thus, her BMI was equal to 16.93. Besides, she had a dry curly frizzy hair.

In physical examination, acanthosis nigricans, hepatosplenomegaly, cardiovascular abnormality and mental retardation were absent. Bone age was measured by Grulich and Pyle method and reported as 7 years.

Laboratory assessments were done. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT) and alkaline phosphatase levels were checked and reported in the normal range. No abnormality detected in thyroid function tests as well as fasting blood sugar (FBS) level, which was 84 mg/dL. Low density lipoprotein (LDL), high density lipoprotein (HDL) and cholesterol levels were in the normal range. Serum triglyceride level was 320 mg/dL, which is elevated. Insulin, LH, FSH and estradiol levels were 23, 5, 1 and 25 μU/mL, respectively.

The ultrasonography of ovaries revealed increased size containing multiple mature follicles. Uterine size was extended, as well. Both of the findings demonstrated early onset of puberty, which is concluded to be central.

Considering the clinical phenotypes and suspicious to BSCL syndrome, different exons and splice junctions of the *AGPAT2* gene were sequenced. The patient was homozygous for the c.514G > A mutation corresponding to the 172nd amino acid change from glutamate to lysine (p.Glu172Lys). Thus, the diagnosis of BSCL syndrome was confirmed for this patient.

3. Discussion

The presented patient is the first case of BSCL syndrome from Iran who carried a homozygous mutation in codon 514 of *AGPAT2* gene. The patient was born from consanguine parents, which is expected as of autosomal recessive inheritance of disease. As the risk of having another affected child is 25% at each pregnancy, a prenatal test could be done chorionic villus sample or amniotic fluid, while carrier testing of family members is also advised. This practice is important, especially in the regions with high rate of consanguinity and increased frequency of autosomal recessive disorders [7].

AGPAT2 mutations usually lead to less severe symptoms in comparison to *BSCL2* gene mutations [8]. Hypertriglyceridemia which is a common finding in CGL patients was detected in our patient, yet no hypercholesterolemia existed. Hapatomegaly, hepatic steatosis and cardiac disorders have been reported frequently in other reports [2,4], whereas they were absent in our case. Muscle pseudo-hypertrophy was detected in our patient, similar to other reports, while acanthosis nigricans and acromegaloid features were absent.

It is noteworthy that female patients are more easily diagnosed and thus are more reported. Polycystic ovaries, oligomenorrhea, irregular menstrual periods, cliteromegaly and hirsutism are common in female patients [2,4,9].

A strict diet with least intake of carbohydrates and fat is the most routine therapeutic approach [1,4]. This method may be beneficial in a short term period, but long-term management would not be easy to hold [4]. Co-administration of Metformin and insulin could be useful in these patients. It decreases the appetite and improves glycemic profile. Besides, menstrual disorders and hepatic steatosis are believed to be reduced in this method [4]. Metreleptin, a recombinant human leptin, is a new therapeutic chance in this syndrome [4,10]. Glycemic control, triglyceride level reduction and liver function improvement are all achieved when CGL patients are treated by metreleptin [4,10].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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