CASE REPORT

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Metreleptin Treatment in a Boy with Congenital Generalized Lipodystrophy due to Homozygous c.465_468delGACT (p.T156Rfs*8) Mutation in the *BSCL2* Gene: Results From the First-year

Şervan Özalkak[1], Meliha Demiral[2], Edip Ünal[3], Funda Feryal Taş[1], Hüseyin Onay[4], Hüseyin Demirbilek[5], Mehmet Nuri Özbek[1]

[1]Gazi Yaşargil Training and Research Hospital, Clinic of Pediatric Endocrinology, Diyarbakır, Turkey
[2]Balıkesir City Hospital, Clinic of Pediatric Endocrinology, Balıkesir, Turkey
[3]Dicle University Faculty of Medicine, Department of Paediatric Endocrinology, Diyarbakır, Turkey
[4]Multigen Genetic Diseases Diagnosis Center, Department of Medical Genetics, İzmir Turkey
[5]Hacettepe University Faculty of Medicine, Department of Paediatric Endocrinology, Ankara, Turkey

What is already known on this topic?

Congenital generalized lipodystrophy is a rare, autosomal recessive disorder characterized by an almost complete absence of body fat. Metreleptin, a preparation of recombinant human leptin, has been suggested as an effective treatment option.

What this study adds?

The presented case is currently the youngest patient from Turkey who was successfully managed using metreleptin treatment. Initiation of metreleptin treatment in the early period may be beneficial in reducing mortality and morbidity and increasing quality of life in patients with congenital generalized lipodystrophy

Abstract

Congenital generalized lipodystrophy (CGL) is a rare, autosomal recessive disorder characterized by an almost complete absence of body fat. In CGL, patients may have hyperphagia due to leptin deficiency. Recombinant human leptin (metreleptin) has been suggested as an effective treatment option. We present successful treatment with metreleptin in a boy with CGL and results from the first year of follow-up. An eight-month-old boy presented with excessive hair growth and a muscular appearance. On examination he had hypertrichosis, decreased subcutaneous adipose tissue over the whole body and hepatomegaly. Laboratory investigations revealed hypertriglyceridemia, hyperinsulinemia, elevated liver transaminases and low leptin levels. Molecular genetic analysis detected a homozygous, c.465_468delGACT (p.T156Rfs*8) mutation in the *BSCL2* gene. A diagnosis of CGL type 2 was considered. Despite dietary intervention, exercise, and treatment with additional omega-3 and metformin, the hypertriglyceridemia, hyperinsulinemia, and elevated liver transaminase levels worsened. Metreleptin treatment was started and after one year hyperphagia had disappeared, and there was dramatic improvement in levels of insulin, hemoglobin A1c, triglycerides and liver transaminases. Hepatosteatosis was lessened and hepatosplenomegaly was much improved. Metreleptin appears to be an effective treatment option in children with CGL that remarkably improved metabolic complications in the presented case. Initiation of metreleptin treatment in the early period may decrease mortality and morbidity, and increase the quality of life in children with CGL.

Keywords: Congenital generalized lipodystrophy, *BSCL2* gene, metreleptin treatment

Address for Correspondence: Şervan Özalkak MD, Gazi Yaşargil Training and Research Hospital, Clinic of Pediatric Endocrinology, Diyarbakır, Turkey
Phone: +90 505 549 98 56 **E-mail:** drservanoz@gmail.com **ORCID:** orcid.org/0000-0002-1557-6040

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Introduction

Congenital generalized lipodystrophy (CGL), also known as Berardinelli Seip syndrome, is a rare, autosomal recessive disorder, usually presenting in the first year of life and characterized by near-total fat atrophy, muscular hypertrophy, and prominent veins (1,2,3,4,5). The prevalence of CGL is estimated as 1:10,000,000 (6). However, the prevalence of CGL in Turkey has been estimated to be much higher at 1:2,000,000 (5). In CGL, hyperphagia associated with leptin deficiency, rapid growth, umbilical hernia, hepatosplenomegaly and acromegalic appearance may be present (1,2,3,7,8).

CGL may cause hyperinsulinemia, hypertriglyceridemia, insulin resistance, diabetes, polycystic ovary syndrome, non-alcoholic fatty liver disease, proteinuria and cardiomyopathy (1,2,3,4,5,6,7). In addition to phenotypic characteristics, evaluation of body fat percentage and distribution, dual-energy X-ray absorptiometer (DXA) and whole-body magnetic resonance imaging may be helpful for the diagnosis of CGL (1,2,7). Low serum leptin levels support the diagnosis, and this finding is also important from the point of view of clinical management (5). Genetic testing is required to confirm the diagnosis and genetic counseling should be given (7). Pathogenic variants in the genes *AGPAT2, Berardinelli-Seip congenital lipodystrophy 2 (BSCL2), CAV1* and *PTRF* cause CGL type 1, type 2, type 3 and type 4, respectively (1).

The goal of the treatment is to prevent metabolic complications and restore cosmetic appearance. Lifestyle changes, including dietary intervention and physical exercise, are the cornerstones of the initial treatment of CGL (1,2,7). When achieving target triglyceride levels with appropriate dietary intervention and exercise is unsuccessful, lipid-lowering drugs may be used (1,2,7). Metformin is the first choice drug for pharmacotherapy when there is insulin resistance. In patients who develop diabetes, insulin may be used in conjunction with metformin treatment (2,7). Many studies have reported the efficacy of recombinant human leptin (metreleptin) in CGL (9,10,11,12). Metreleptin reduces appetite through leptin receptors in the hypothalamus (13) and improves peripheral and hepatic insulin sensitivity (14). Metreleptin reduces hyperphagia, triglyceride, and hemoglobin A1c (HbA1c) levels and improves hepatic steatosis. In the present case report, presenting features, diagnosis and the first-year results of a male with CGL type 2 due to a homozygous pathogenic variant in the *BSCL2* gene and treated with metreleptin are presented.

Case Report

The eight-month-old boy presented with excessive hair growth and a muscular appearance over the whole body. He was born to first cousins after a term, uneventful gestation via spontaneous vaginal delivery. His birth weight was 3100 g. On physical examination performed at the time of presentation his weight was 9 kg [0.09 standard deviation score (SDS)], height was 73.8 cm (0.92 SDS), body mass index was 16.5 kg/m^2 (-0.64 SDS) and blood pressure was 80/50 mmHg (Table 1). Remarkable hypertrichosis was present on the extremities, waist and hips. The muscular appearance was prominent on his arms, and reduced subcutaneous adipose tissue was observed in the face and whole body. The abdomen was distended with enlarged liver (5-6 cm palpable), spleen (3-4 cm palpable) and umbilical hernia. Testicular volume was 2/2 mL, pubic and axillary hair were at Tanner stage 1, and stretched penile length was 6 cm. Diagnosis and follow-up images are presented in Figure 1. On laboratory investigation, glucose was 95 mg/dL, insulin 36.5 mIU/mL, HbA1c 5.9%, triglyceride 218 mg/dL, total cholesterol 162 mg/dL, and liver transaminases

Figure 1. Images of the case before (a, b) and first year (c, d) treatment with metreleptin

Table 1. The follow-up data before and after metreleptin treatment

	At diagnosis	F/up visit 1	F/up visit 2	F/up visit 3	F/up visit 4 (metreleptin initiated)	F/up visit 5	F/up visit 6	F/up visit 7	F/up visit 8 (first year of metreleptin treatment)	% difference (after 1 year treatment)
Age (years)	0.75	3.75	4.75	5.25	5.5	5.75	6	6.25	6.5	
Height SDS	0.92	2.42	2.88	3.04	3.2	3.1	3.3	3.13	3.06	-4.3
BMI SDS	-0.64	2.75	2.52	2.4	2.3	1.63	1.53	0.9	1	-56
Fasting glucose (mg/dL)	95	92.5	105	68	135	78	81	70	85	-37
Fasting insulin (mIU/mL)	36.5	54.2	65	151	185	2.42	21	10	12	-93
HbA1c (%)	5.9	6.2	6.7	7.6	6.7	5.6	5.1	5.1	5.2	-22
Triglyceride (mg/dL)	218	192	248	208	197	38.3	88		85	-66
Total cholesterol (mg/dL)	162	119	131	136	162	131	118		120	-25
LDL cholesterol (mg/dL)	104	68	85	81	100	69	60		70	-30
HDL cholesterol (mg/dL)	7	21.3	25	41	26	50	42		41	+36
ALT (U/L)	309	257	380	747	482	45	42	18	31	-93
AST (U/L)	267	147	254	342	306	33	41	21	29	-90
Liver size (mm)	101	137	195		195	170			167	-14
Spleen size (mm)	70	124	130		142	134			121	-15
Bone age (years)					8.5					
Echocardiography	Normal				Normal				Normal	
Treatment	Diet	Diet, exercise, metformin	Diet, exercise	Diet, exercise	Diet, exercise, metreleptin	Diet, exercise, metreleptin	Diet, exercise, metreleptin	Diet, exercise, metreleptin	Diet, exercise, metreleptin	

F/up: follow-up, BMI: body mass index, HbA1c: glycated hemoglobin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDL: low-density lipoprotein, HDL: high-density lipoprotein, SDS: standard deviation score

were elevated with an alanine aminotransferase of 309 U/L and an aspartate aminotransferase of 267 U/L. His leptin level (0.19 ng/mL) was low (Table 1).

Molecular Genetic Analysis

Genomic DNA was isolated from peripheral blood cells using standard techniques. Mutation analyses were performed by bidirectional sequencing of the coding exons and the exon-intron boundaries of the *AGPAT2* and *BSCL2* genes. Polymerase chain reaction primers used in order to amplify the regions of interest are available upon request. Sequencing was performed with Miseq V2 chemistry on Illumina MiSeq Sequencer (Illumina, CA, USA). Analysis was performed with IGV software. Molecular genetic analysis unveiled a homozygous, c.465_468delGACT (p.T156Rfs*8) pathogenic variant in the *BSCL2* gene, and a diagnosis of CGL type 2 (Berardinelli-Seip syndrome) was considered (Figure 2). This pathogenic variant has been previously reported (5).

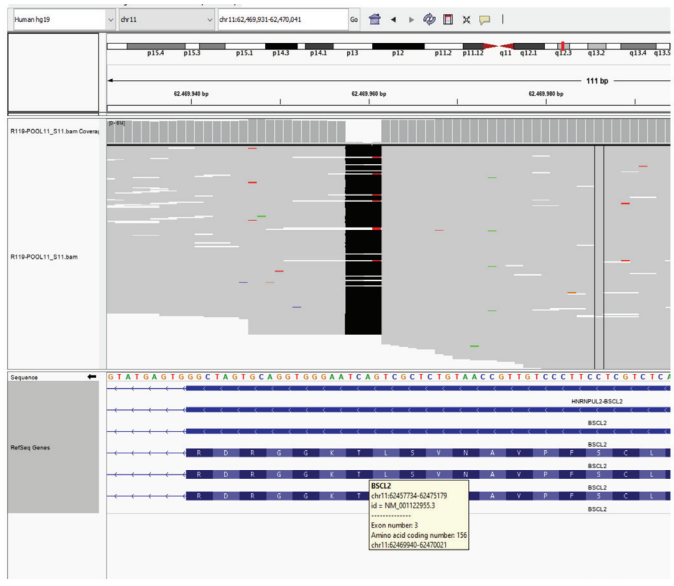

Figure 2. Molecular genetic analysis of the case *BSCL2* c.465_468del (p.T156Rfs*8)

Treatment and Follow-up Characteristics

Initial management was attempted with lifestyle modification. However, dietary adherence was poor due to hyperphagia and his clinical (marked hepatosplenomegaly and hepatosteatosis) and biochemical (increase in triglyceride levels, insulin resistance, and HbA1c levels) features had worsened. Metreleptin treatment was considered at this time but was not commenced due to rejection of social security institution rules for reimbursement. Therefore, metformin treatment was delayed for several years. During this time, and despite dietary intervention, exercise, omega-3 supplementation and metformin treatments, hypertriglyceridemia, insulin resistance, liver transaminase levels and hepatosteatosis did not improve. Eventually, when he was five and a half years-old, metreleptin treatment was initiated at a subcutaneously administered dose of 0.06 mg/kg/day. Metreleptin treatment improved his sense of satiety, and he achieved weight loss, thereby restoring metabolic parameters including normal triglyceride, insulin, HbA1c and liver transaminase levels. The size of the liver and the spleen and abdominal distension decreased. The follow-up data after metreleptin treatment are presented in Table 1. The patient did not develop cardiomyopathy, arrhythmia, or proteinuria although neurodevelopmental delay was present. Informed consent was obtained from the patient's parents for publication and the use of photos.

Discussion

We report successful management of metabolic complications in a child with CGL2 due to a homozygous c.465_468delGACT (p.T156Rfs*8) mutation in the *BSCL2* gene. CGL2 (OMIM #269700) is caused by pathogenic variants of the *BSCL2* gene (1), which encodes for the transmembrane protein seipin. This protein is involved in the fusion of small lipid droplets in adipocytes and also in adipocyte differentiation (1,2). Low serum leptin levels may help to confirm the diagnosis and determine the management strategies (5). A relatively high concentration of adiponectin is a differential feature of CGL2, while serum leptin levels are extremely low in all subtypes of CGL (5). In our case, the leptin level was low and the response to metreleptin treatment was excellent.

Early-onset hyperphagia associated with leptin deficiency, rapid growth, advanced bone age, umbilical hernia, hepatosplenomegaly, and acromegalic appearance are among the clinical features of CGL (1,2,3,7,8). The present case had excessive growth of body hair, a muscular appearance, prominent veins due to absence of subcutaneous fat, hepatosplenomegaly and umbilical hernia at the time of the diagnosis. Hyperphagia appeared after the age of one year (Figure 1).

However, avoiding excess calorie intake, adjusting dietary fat content to manage hypertriglyceridemia, and increasing monounsaturated fat and long-chain fatty acids and in selected cases lipid-lowering drugs may be part of the treatment (1,2,7). The present case had insulin resistance, hypertriglyceridemia and hepatosteatosis at diagnosis. He was poorly adherent to the nutrition plan because of his hyperphagia. Metformin is the first choice drug in patients with severe insulin resistance, but it is not yet been approved for children under the age of 10 years. In patients with CGL who develop diabetes, insulin in combination with metformin, may be required. Moreover, the insulin therapy may need to be extremely high-dose (>100 units/day) because of the severity of insulin resistance in these patients (2,7). In the present case, an off-label use of metformin was done with consent family, while it was stopped due to lack of a clinical or biochemical improvement. Metreleptin regulates appetite and also improves peripheral and hepatic insulin sensitivity, partially independent of food intake (13,14,15,16). It also normalizes gonadotropin secretion, reduces proteinuria, improves immune function and lowers androgen levels, particularly in lipodystrophic females with polycystic ovary syndrome (17).

In this case, metreleptin treatment was initiated at the age of five and a half, which successfully decreased hyperphagia with a dramatic improvement in metabolic parameters, including insulin resistance, and triglyceride and liver transaminase levels, while HbA1c level reduced to within normal ranges. Hepatosteatosis improved with a remarkable decrease in the size of the liver and the spleen (Table 1). Furthermore, no side effects associated with metreleptin treatment were observed.

Conclusion

To the best of our knowledge, the present case is the youngest patient with CGL2 in Turkey to be successfully managed using metreleptin treatment. In children with CGL, metreleptin seems to be the most effective treatment option for preventing the development of metabolic complications. We suggest that initiation of metreleptin treatment in the early period may decrease mortality and morbidity due to the dramatic improvement seen in markers of metabolic derangement, as well as improvement of the quality of life in CGL patients.

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Ethics

Informed Consent: Informed consent was obtained from the patient's parents for publication and the use of photos.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Şervan Özalkak, Meliha Demiral, Edip Ünal, Funda Feryal Taş, Hüseyin Demirbilek, Concept: Şervan Özalkak, Funda Feryal Taş, Hüseyin Onay, Mehmet Nuri Özbek, Design: Şervan Özalkak, Funda Feryal Taş, Hüseyin Onay, Mehmet Nuri Özbek, Data Collection or Processing: Şervan Özalkak, Meliha Demiral, Edip Ünal, Funda Feryal Taş, Hüseyin Onay, Hüseyin Demirbilek, Mehmet Nuri Özbek, Analysis or Interpretation: Şervan Özalkak, Hüseyin Onay, Hüseyin Demirbilek, Mehmet Nuri Özbek, Literature Search: Şervan Özalkak, Hüseyin Demirbilek, Writing: Şervan Özalkak, Hüseyin Onay, Hüseyin Demirbilek.

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