Case report

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

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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 has been suggested as an effective treatment option.

What this study adds?
The present case is the youngest patient in Turkey who has been successfully managed using metreleptin treatment. Initiation of metreleptin treatment in the early period may closely related with decreased mortality and morbidity and increase quality of life in CGL patients.

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, herein, present the successful use of metreleptin in a case with CGL and its 1-year follow-up. An eight-month-old boy presented with complaints of hair growth and muscular appearance: He had, hypertrichosis, decreased subcutaneous adipose tissue in the whole body and hepatomegaly. In the laboratory investigations hypertriglyceridemia, hyperinsulinemia, elevated liver transaminases and low leptin levels were detected. In molecular genetic analysis homozygous c.465_468delGACT (p.T156Rfs*8) mutation was detected in the BSCL2 gene. A diagnosis of CGL type 2 was considered. Despite the dietary intervention, exercises, omega-3 and metformin treatment, the hypertriglyceridemia, hyperinsulinemia, and elevated liver transaminase levels worsened. After one year of metreleptin treatment, hyperphagia disappeared, insulin, HbA1c, triglyceride and liver transaminase levels improved dramatically. Hepatosteatosis reduced, The size of the liver and the spleen remarkably decreased. Metreleptin is an effective treatment option that prevents the development of metabolic complications of CGL in children. The initiation of metreleptin treatment in the early period would decrease mortality and morbidity, and increase the quality of life in children with CGL.

Keywords: Congenital generalized lipodystrophy, BSCL2 gene, Metreleptin treatment

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Introduction
Congenital generalized lipodystrophy (CGL), also known as Berardinelli Seip syndrome, is a rare autosomal recessive disorder presented in the first year of life and characterized by near-total fat atrophy muscular hypertrophy, and prominent veins (1, 2, 3, 4, 5). Its prevalence is estimated as 1:10 million (6). The prevalence of CGL in Turkey has been reported as 1.2 million (5). In CGL, hyperphagia associated with leptin deficiency, rapid growth, umbilical hernia, hepatosplenomegaly, and acromegalic appearance may be present (6, 7, 8).

CGL may cause hyperinsulinemia, hypertriglyceridemia, insulin resistance, diabetes, polycystic ovary syndrome, non-alcoholic fatty liver disease, proteinuria, and cardiomyopathy (1-7). In addition to phenotypic characteristics, evaluation of body fat percentage and distribution, dual-energy X-ray absorptiometer (DXA) and whole-body magnetic resonance imaging can be used in the diagnosis of CGL (1, 2, 7). Low serum leptin levels support the diagnosis, which is also important from the management point of view (5).

Genetic testing is required to confirm the diagnosis and provide genetic counselling (7). Pathogenic variants in AGPAT2, BSCL2, CAV1, and PTRF genes 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 cornerstone of the initial treatment of CGL (1, 2, 7). In case of failure in achieving target triglyceride levels with appropriate dietary intervention and exercise, lipid-lowering drugs may be used (1, 2, 7). Metformin is the first choice drug for pharmacotherapy in case of insulin resistance. In patients who develop diabetes, insulin may be used along with metformin treatment (2, 7). The efficacy of recombinant human leptin (metreleptin) in CGL has been shown in many studies (9-12). Metreleptin reduces appetite through leptin receptors in the hypothalamus (13) and improves peripheral and hepatic insulin sensitivity (14). Metreleptin reduces hyperphagia, triglyceride and HbA1c levels and improves hepatic steatosis. In the present case report, we assessed the first-year results of metreleptin treatment in a male with CGL type 2 due to a homozygous pathogenic variant in the BSCL2 gene.

Case: The eight-month-old boy presented with hair growth and a masculine appearance on 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 the physical
examination performed at the time of the presentation his weight was 9 kg (0.09 SDS), height was 73.8 cm (0.92 SDS), BMI was 16.5 kg/m² (-0.64 SDS) and BP was 80/50 mmHg (Table 1). Remarkable hypertrichosis was present on the extremities, waist and hips. The masculine appearance was evident on the 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 were presented in Figure 1. Table 1. In the laboratory investigations, glucose was 95 mg/dL, insulin 36.5 mIU/mL, HbA1c 5.9%, triglyceride 218 mg/dL, total cholesterol 162 mg/dL, ALT 309 U/L and AST 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. PCR primers used in order to amplify the regions of interest were available upon request. Sequencing was performed with MiSeq V2 chemistry on Illumina MiSeq Sequencer (Illumina California, USA). Analysis was performed with IGV software. In the molecular genetic analysis, a homozygous c.465_468delGACT (p.T156Rfs*8) pathogenic variant was detected in the BSCL2 gene, and a diagnosis of CGL type 2 (Berardinelli-Seip syndrome) was considered (figure2). The pathogenic variant detected in our case has been previously reported (1).

**Treatment and follow up characteristics**

We first tried managing the case with lifestyle modification. However, dietary adherence was poor due to hyperphagia. The clinical (marked hepatosplenomegaly and hepatosteatosis) and biochemical (increase in triglyceride levels, insulin resistance, and HbA1c levels) features had worsened. Metreleptin treatment was considered while not commenced due to rejection of social security institution rules for reimbursement. Therefore, metformin treatment was initiated when he became four years old. Despite the dietary intervention, exercise, omega-3 and metformin treatments, hypertriglyceridemia, insulin resistance, liver transaminase levels and fatty liver did not improve. When the patient 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 the sense of satiety, and achieved weight loss, thereby restored metabolic parameters suggesting a normal triglyceride, insulin, HbA1c and liver transaminases. 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 while a neurodevelopmental delay was present. Informed consent was obtained from the patient’s parents for publication and the use of photos.

**Discussion**

In the present case report, we report successful management of metabolic complications in an infant 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 Berardinelli-Seip congenital lipodystrophy 2 (BSCL2) gene (1), which encodes for a 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. In addition to phenotypical characteristics, and anthropometric measurements, assessment of the amount and distribution of body fat using dual-energy X-ray absorptiometer (DXA) or whole-body magnetic resonance imaging are adjunctive diagnostic tools for the diagnosis of CGL (1, 2, 7). Genetic testing is required to confirm the diagnosis and to provide genetic counselling (7).

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 (1-3, 7, 8). Our patient had excessive body hair growth, masculine appearance, phlebomegaly, hepatosplenomegaly and umbilical hernia at the time of the diagnosis. Hyperphagia appeared after the age of one year (Figure 1). The goal of treatment is to prevent metabolic complications and to improve cosmetic appearance. Lifestyle changes including dietary intervention and physical exercise are the mainstay of the treatment of CGL (1, 2, 7)

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). Our patient had insulin resistance, hypertriglyceridemia and hepatosteatosis at the diagnosis, whereas, adherence to the nutrition plan could not be achieved due to hyperphagia which was developed after the age of one. Metformin is the first choice drug in patients with severe insulin resistance. However, metformin has not yet been approved for children under the age of 10 years. In patients who develop diabetes insulin, in combination with metformin, may require. Moreover, an extremely high-dose insulin therapy (>100 units/day) may be required due to severe insulin resistance (2, 7). Metreleptin regulates appetite through leptin receptors in the hypothalamus (13). Metreleptin also improves peripheral and hepatic insulin sensitivity, partially independent of food intake (14). It also normalizes gonadotropic secretion, reduces proteinuria, improves immune function and lowers androgen levels (particularly in lipodystrophic females with HPO) (4).

In our patient, metreleptin treatment was initiated at the age of five, which successfully decreased hyperphagia with a dramatic improvement in metabolic parameters including insulin resistance, triglyceride and liver transaminase levels. The HbA1c level declined to normal ranges. Hepatosteatosis was reduced 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.

To the best of our knowledge, the present case is the youngest patient in our country who has been 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. Therefore, initiation of metreleptin treatment in the early period may be closely related to decrease in the mortality and morbidity as well as improvement of the quality of life in CGL patients.

**Acknowledgements**

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**References**

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<th>F/up visit 1</th>
<th>F/up visit 2</th>
<th>F/up visit 3</th>
<th>F/up visit 4 (Metreleptin initiated)</th>
<th>F/up visit 5</th>
<th>F/up visit 6</th>
<th>F/up visit 7</th>
<th>F/up visit 8 (First year of metreleptin treatment)</th>
<th>% difference (after 1 year treatment)</th>
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F/up: Follow-up  
BMI: Body mass index  
HbA1c: glycated hemoglobin  
ALT: alanine aminotransferase  
AST: aspartate aminotransferase
Figure 1. Images of the case before (a, b) and first year (c, d) treatment with metreleptin.

Figure 2. BSCL2 c.465_468del (p.T156fs*8)