

Congenital Generalized Lipodystrophy Type 2 in a Patient From a High-Prevalence Area

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Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disease characterized by the loss of body fat. The global prevalence of CGL is one in 10 million, and there are four subtypes. The case is presented of a 18-year-old woman from rural area of the north coast of Peru (Piura) with limited access to health services. She was diagnosed with phenotypic CGL at age 7 months. At age 12 years, she was diagnosed with diabetes and had altered liver function tests. She underwent a liver biopsy, which revealed advanced portal fibrosis. The patient stopped attending evaluations for 3 years; subsequently, she was referred to Dos De Mayo Hospital in Lima. Physical examination revealed typical triangular facies, acanthosis nigricans, and hirsutism; little subcutaneous tissue; proximal muscle weakness with stiffness in joints; and clitorimegaly. As of this writing, the patient is waiting to initiate outpatient therapy with a leptin analog. She has physical characteristics of CGL type 2 and a natural progression of the disease that presents cirrhosis caused by nonalcoholic fatty liver disease. She lives in a region of high CGL type 2 prevalence, which, without treatment, has a poor prognosis. Liver failure is the main cause of death. There are barriers for this group of patients to access the best treatment and one purpose of this report is to attract the attention of health institutions to help us treat these patients.

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Congenital generalized lipodystrophy (CGL) is a rare autosomal recessive disease characterized by the loss of body fat. The prevalence of CGL is one in 10 million [1]. There are four distinct subtypes of CGL: Type 1 is associated with *AGPAT2* mutations; type 2 is associated with *BSCL2* mutations; type 3 is associated with *CAVI* mutations; and type 4 is associated with *PTRF* mutations. [2] The four subtypes share the following characteristics: loss of body fat tissue, accelerated growth, insulin resistance, hypertriglyceridemia, and nonalcoholic fatty liver disease.

In our country, there are recent reports of people with CGL type 2 who are from Piura [3]. High CGL incidence has been reported in patients with European and Middle Eastern origins [4, 5].

1. Clinical Case

An 18-year-old woman from rural area of the north coast of Peru (Piura), where there is limited access to health services, was diagnosed with phenotypic CGL at age 7 months. Her health assessments have been irregular since then. She was diagnosed with diabetes at age 12 years, and had mixed dyslipidemia and altered liver function tests. She underwent a liver biopsy, which revealed advanced portal fibrosis.

The patient stopped attending evaluations for 3 years. When her diabetes became uncontrolled and she had hypertriglyceridemia, she was referred to Dos De Mayo Hospital in Lima.

Abbreviation: CGL, congenital generalized lipodystrophy.

At physical examination, that patient had typical triangular facies, acanthosis nigricans, and hirsutism; little subcutaneous tissue; proximal muscle weakness with stiffness in joints (Fig. 1); and clitorimegaly. She has psychomotor retardation and moderate cognitive impairment.

An abdominal ultrasound indicated hepatomegaly and a 13-mm portal vein. She started treatment with NPH insulin with optimal glycemic control. As of this writing, the patient is waiting to begin outpatient leptin analog therapy.

2. Discussion

Although this patient did not undergo genetic testing, we know the variant of CGL she has, because five patients from the same region of our country had sequencing of the *BSCL2* gene, known to be mutated in type 2 CGL (or Berardinelli–Seip syndrome). Sequencing revealed a homozygous deletion of exon 3 in all five patients, suggesting the presence of a founder mutation. The diagnosis of CGL was supported by other clinical characteristics, such as overly muscular appearance, prominent superficial veins, pseudoacromegaloid features, and metabolic abnormalities associated with insulin resistance and, most important, liver failure that corresponds to CGL type 2, and absence of adipose tissue in the palms, soles, scalp, or orbital region as compared with patients with type 1 CGL. Also, this patient has psychomotor retardation and moderate cognitive impairment, which are more frequent in CGL type 2 [3, 6].

The *BSCL2* mutation encodes a protein called seipin that is critical for normal adipogenesis and induction of the expression of key lipogenic transcription factors. Individuals with type 2 *BSCL2* seem to present more severe and premature symptoms than those who have mutations in type 1. There is a higher incidence of intellectual deficiency in type 2 *BSCL2* that can be explained by the fact that seipin is expressed variably in several tissues, such as liver,



Figure 1. Photographs of the patient in this case report. (Top row, left to right) The patient exhibits lipodystrophy, marked muscle hypertrophy, hirsutism, and typical triangular facies. (Bottom row, left to right) The patient has little subcutaneous tissue and has stiffness in her joints.

skeletal muscle, kidney, pancreas, and testicles, and is highly expressed in the central nervous system, whereas *AGTPA2* is a tissue-restricted enzyme, occurring at high levels in adipose tissue, liver, and cardiac tissue but almost undetectable in the brain [7].

The high cost of leptin analogs has been the main barrier for this group of patients to access the treatment to improve their quality of life [8]. Several studies have reported the use of recombinant leptin in CGL. The first studies in adults with lipodystrophy showed that leptin replacement therapy improved glycemic control and decreased triglyceride levels, thereby allowing for the discontinuation or a large reduction in antidiabetes therapy. They also proved that leptin treatment was able to correct hepatic steatosis and reverse insulin resistance, with benefits sustained for at least 12 months of treatment. Metreleptin has been demonstrated to improve metabolic abnormalities in patients with CGL. We are trying to get the patient in this case report into clinical trials or an institution that provides treatment with these orphan drugs.

This case is related to the high prevalence of CGL in this part of our country. We want to attract the attention of health institutions to help us treat our patients who have a worse outcome because they have a more severe type of lipodystrophy [9].

In conclusion, we present the case of a patient with physical characteristics of CGL type 2 and a natural progression of the disease that presents cirrhosis caused by nonalcoholic fatty liver disease. This patient lives in a region of high CGL type 2 prevalence where, without treatment, the prognosis is poor and severe liver failure is the main cause of death.

There are barriers for this group of patients to access the best treatment; thus, one of the purposes of this report is to attract the attention of health institutions to help us treat these patients.

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