

Congenital Generalized Lipodystrophy

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Article Info

Article Notes

Received: April 02, 2018

Accepted: May 11, 2018

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Keywords

Lipodystrophy
Berardinelli-Seip syndrome
Diabetes
Hypertriglyceridemia

ABSTRACT

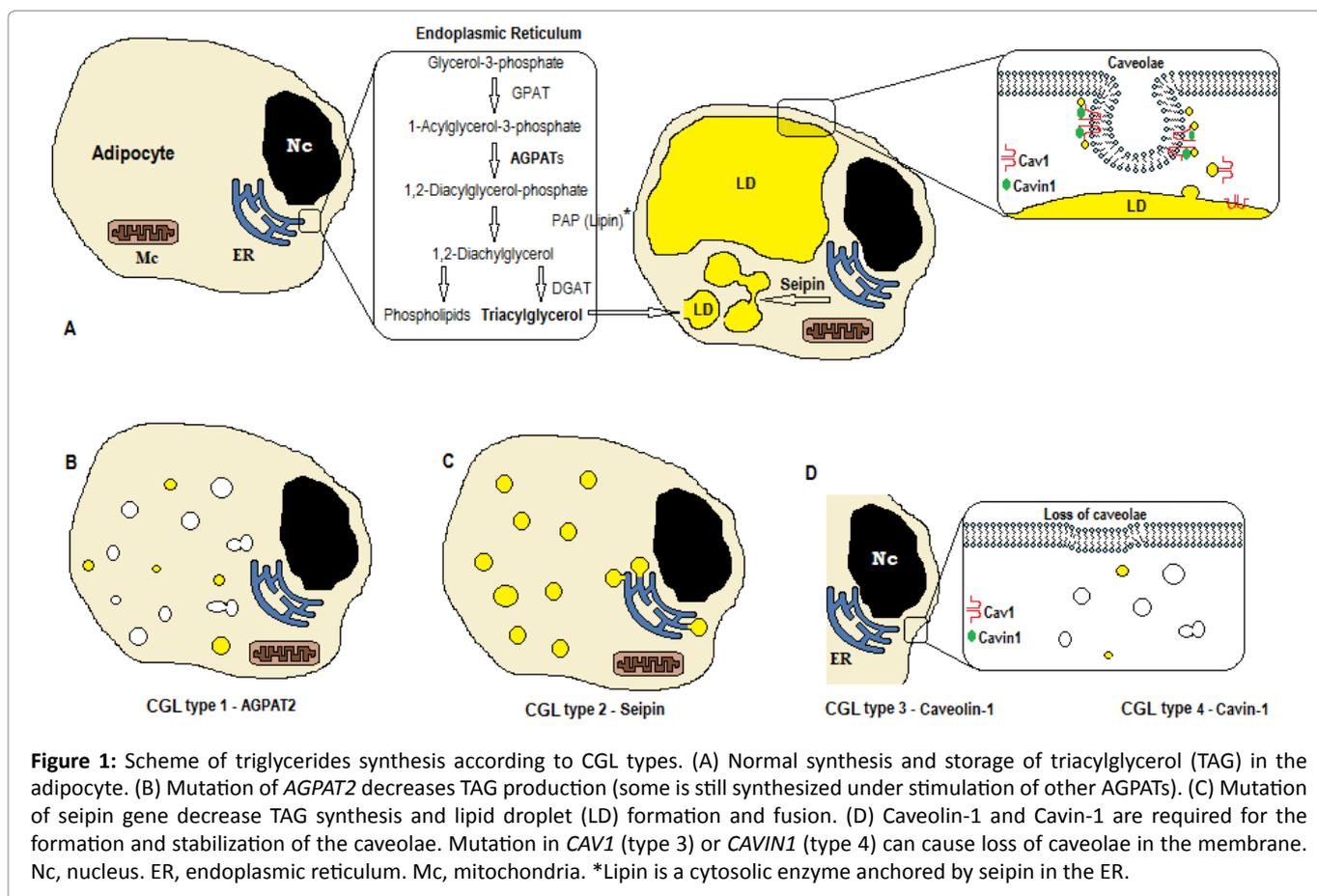
Congenital Generalized Lipodystrophy (CGL) is a rare and severe autosomal recessive disease. Patients are defective in the storage of body fat and, consequently, they deposit fat in ectopic tissues, mainly liver, and can develop cirrhosis. Insulin resistance is a typical finding, causing diabetes that require high daily doses of insulin. In the state of Rio Grande do Norte, Brazil, we have one of the largest cohorts of patients with CGL. In this article, we review pathophysiology, clinical picture and treatment of this disease.

Introduction

Type 2 diabetes is a world health problem, and usually results from excessive weight and increased visceral fat causing peripheral insulin resistance and an inability of the pancreas to release insulin to compensate this resistance. Other less common types of diabetes occur due to specific genetic mutations, like the Congenital Generalized Lipodystrophy (CGL), also known as Berardinelli-Seip Congenital Lipodystrophy (BSCL). CGL is an autosomal recessive disease that is classified into four types, based on gene mutation. The altered genes play essential functions for adipocyte formation, lipid production and proper storage inside the adipocyte. The mutations decrease adipose tissue with consequent deposition of fat in ectopic sites, causing fat liver, altered carbohydrate metabolism, severe insulin resistance with hyperinsulinemia and acromegaloïd features, and dyslipidemia¹⁻³. The CGL syndrome has around 500 cases reported in the world. In Brazil, in the State of Rio Grande do Norte (RN), we have diagnosed, treated, and followed 54 cases in the past 20 years^{4, 5}. In a descriptive study using secondary data, we estimated a total of 103 patients in RN⁶. This indicates a much higher prevalence than that reported in the literature (1: 1 million)⁷.

Triacylglycerol formation and storage in lipid droplets

The biosynthesis of triglycerides and phospholipids (Figure 1A) starts with glycerol-3-phosphate acyltransferase (GPAT) acylating the glycerol-3-phosphate in position 1, forming 1-Acylglycerol-3-phosphate (lysophosphatidic acid). It is followed by another acylation step at position two by the enzyme AGPAT (1-Acylglycerol-3-phosphate acyltransferase), originating 1,2-Diacylglycerol-3-phosphate (phosphatidic acid). It is a key intermediate step in the biosynthesis pathway of both triglycerides and phosphoglycerides. There are 11 isoforms of AGPAT enzymes, encoded by different genes⁴. AGPAT1 and AGPAT2 are the most extensively studied. AGPAT1 is present at high levels in testis, pancreas, and, to a lesser extent, in



adipose tissue and other tissues like heart, placenta, brain, lung, whereas *AGPAT2* is abundant in fatty tissue. In the following steps, the cytosolic enzyme phosphatidic acid phosphatase (PAP or lipin) originates 1,2-diacylglycerol, and the 1,2-diacylglycerol acyltransferase (DGAT) forms triacylglycerol⁴. Phosphatidic acid and diacylglycerol can also originate other phospholipids such as cardiolipin, phosphatidylinositol, and phosphatidylcholine.

Those reactions occur in the adipocytes' endoplasmic reticulum (ER), where a progressive accumulation of triglycerides causes the formation of small lipid droplets (LD)⁸. The product of the gene *BSCL2* is a transmembrane protein called seipin that causes the fusion of small LD, originating large LD. Seipin resides in the ER and concentrates at the junction with nascent LD, facilitating the lipid traffic between ER and LD and the incorporation of triglycerides in LD⁹. Seipin may also act as an ER anchor to the cytosolic enzyme lipin 1. Besides being necessary for lipid droplet fusion, size, and morphology, seipin is also essential for adipogenesis (via interaction to lipin 1) and cellular triglyceride lipolysis^{10, 11}. Deficiency of seipin does hamper the differentiation of pre-adipocytes to adipocytes and affects the final maturation⁹, as shown by studies in mesenchymal stem cells with *BSCL2* knocked out¹². Non-adipose tissues also express seipin, and other functions are to be determined.

In the adipocytes, caveolae, which are specialized 50-100nm membrane invaginations, account for 20% of the plasma membrane area, making the adipocytes the cells with the highest density of caveolae¹³. The formation of lipid droplets needs a membrane protein (Caveolin - the main component of caveolae membranes) and a cytoplasmic protein (Cavin-1)¹⁴. The genes *CAV1*, *CAV2*, and *CAV3* encode three forms of caveolin with similar structures (Caveolin-1, Caveolin-2, and Caveolin-3, respectively). Caveolin-1 and Caveolin-2 are present in adipocytes, fibroblast, and endothelial cells, and Caveolin-3 is present only in skeletal and cardiac muscle^{13, 15}. Caveolin-1 is the most important and the most studied. It is expressed in two different isoforms (1a and 1b). Caveolin-1 translocates from the plasma membrane to lipid droplet, being necessary to lipid trafficking and metabolism¹⁶. Lipid droplets store triglycerides after feeding and these molecules are hydrolyzed to fatty acid, and released during fasting; this mechanism may be regulated by Caveolin-1¹⁶. Caveolin-1 deficiency also increases susceptibility to cell death by autophagy¹⁷.

The gene *CAVIN1* encodes a cytoplasmic protein called caveolae associated protein 1 (Cavin-1)^{14, 16}, that is obligatory for the formation and stabilization of caveolae. Cavin-1 is expressed in adipocytes, muscle cells, and

other cells, and is also essential in the transmission of caveolae-originated signals^{14,18}. Knockout of the *CAV1* gene causes a lack of caveolae in non-muscle cells, whereas the knockout of *CAVIN1* causes the absence of caveolae in all tissues, including muscle¹⁴. The lack of caveolae can affect regulation of lipolysis, fatty acid flux, triglyceride synthesis, and the signals of other pathways.

Types of CGL

Based on detectable genetic alterations, four types are described. Types 1 and 2 are responsible for over 95% of cases, and type 2 has a more severely affected phenotype. Only one case of type 3 and around 30 cases of type 4 have been reported⁴.

CGL Type 1. In 1999, Garg et al. described patients' mutation on chromosome 9q34, and three years later Agarwal et al. showed *AGPAT2* as the enzyme affected by this mutation^{2, 19}. Due to mutation of this *AGPAT2*, none or minimal production of triacylglycerol happens by the stimulus of other isoforms. The phenotype of *AGPAT2* knockout mice is similar to that of humans with CGL type, confirming the role of this enzyme in the pathophysiology^{20, 21}.

CGL Type 2. Magre et al. were the first to identify the mutation in the seipin gene (chromosome 11q13)³. Mutations (mostly nonsense) of the seipin gene (*BSCL2*) produce a truncated protein and can affect lipid metabolism by different mechanisms: a) decrease in

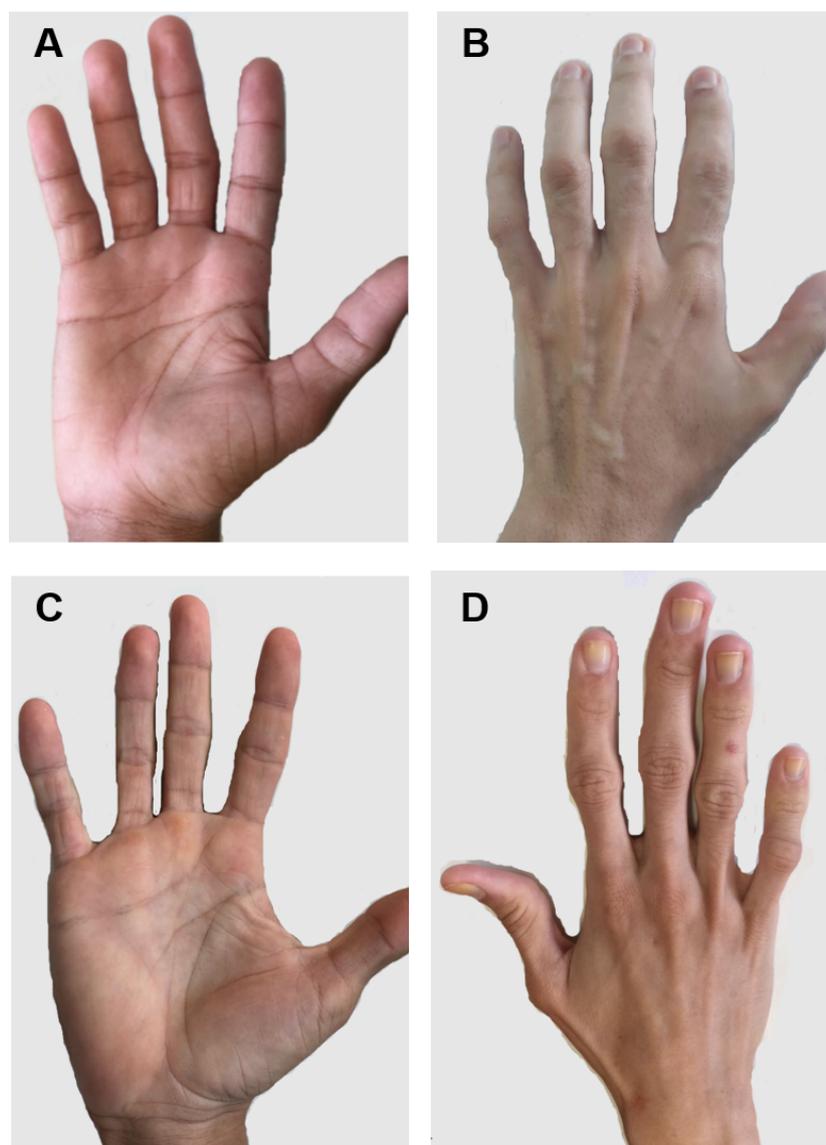


Figure 2: Hands of patients with CGL types 1 and 2. (A) and (B) Anterior and posterior views of hands of type 1 patients. Apparently normal hands, since there is still mechanical fat tissue. (C) and (D) Anterior and posterior views of hands of type 2 patients. The severity of the disease is greater, and the lack of fat is evident and easily noticeable.

seipin stability; b) reduction in ability to bind lipin 1; and c) failure to oligomerize and localize itself exclusively to the ER membrane¹¹. Some cells are still able to generate triacylglycerol and small lipid droplets, but large lipid droplets are absent due to loss of the ability of fusion of these small lipid droplets. There is also a failure in the expression of adipogenic factors, such as the peroxisome proliferator-activated receptor gamma (PPARG), as well as adiponectin and adipocyte fatty acid binding protein (FABP4)^{11, 16}. Seipin deficiency impairs adipogenesis, increases lipolysis, and prevents triglycerides accumulation in adipocytes.

CGL type 3. This type was described recently in a patient who despite having CGL phenotype did not have mutations in genes *AGPAT2* or *BSCL2*²². Mice with a mutation in *Cav1* are resistant to diet-induced obesity and have insulin resistance, hypertriglyceridemia, decreased adiponectin, reduced fat mass, and small adipocytes¹⁶. After choosing candidate genes based on studies in mice, Kim et al. confirmed the presence of a nonsense mutation in the caveolin-1 gene (*CAV1*), on chromosome 7q31²².

CGL type 4. In this is a rare type the affected gene is the *CAVIN1*, which encodes the protein Cavin-1. In humans, it has been reported in patients with generalized congenital lipodystrophy and muscular dystrophy^{15, 23}.

Recently, mutations in the *PCYT1A* and *PPARG* genes have also been described causing lipodystrophy^{24, 25}.

Clinical features

CGL patients usually present acromegaloid facies, acanthosis nigricans, phebomegaly, hepatomegaly, and muscular hypertrophy^{5, 26, 27}. Several authors cite umbilical hernia as a clinical finding of the syndrome²⁶. We evaluated the frequency of it in our series of patients, and none of them presented this change²⁸. In fact, the absence of periumbilical adipose tissue causes protrusion of the umbilical scar, and this may be mistakenly diagnosed as a hernia^{28, 29}.

Once adipocytes cannot adequately store fat, it accumulates in other tissues such as liver, and muscles, causing severe insulin resistance. Bone densitometry (DXA) may show normal or high bone mineral density³⁰ and reduced total body fat (usually lower than 6%)²⁷. As a consequence of low body fat, serum adiponectin and leptin are low too²⁷. As leptin is essential in controlling hunger, these patients typically have hyperphagia, which is readily apparent since childhood. Adiponectin plays an important role as an insulin sensitizer, and its lack worsens the insulin resistance. Despite this, initially, glucose and glycated hemoglobin are normal at the expense of very high insulin levels. Diabetes usually starts at puberty; in our series, the mean age of onset was 15.8±7.1 years²⁷. Initially, they are controlled with oral drugs, needing high doses of insulin in

a few years²⁷. Arterial hypertension occurs in one-third of patients²⁷.

There are some specific clinical features of each CGL type. Patients with type 1 still present mechanical adipose fat, especially in palms, soles, orbital, peri-articular regions³¹. In contrast, type 2 patients show an absence of metabolic and mechanical fatty tissues. Seipin is highly expressed in the brain and cerebellum and is also involved in the regulation of neural functions. More than half of type 2 patients have some cognitive impairment^{1, 8}. Types 3 and 4 have preservation of mechanical and bone marrow fat, and type 4 has muscle weakness associated with high serum creatine kinase and spinal instability¹⁵.

There are also gender-specific clinical features. Polycystic ovaries and amenorrhea are common³². Menstrual cycles usually return to normal with the use of metreleptin, probably due to improvement in insulin sensitivity and restoration of LH pulsatility³². Type 2 men can have teratozoospermia due to the lack of seipin in germ cells³³.

Hypertriglyceridemia occurs since the first years of life and can cause acute pancreatitis. HDL is usually lower than 30 mg/dL. Elevations of liver enzymes is also an early finding and come from the fat deposition in the liver. Progressive reductions in serum platelets suggest worsening of the liver disease and probable cirrhosis³⁴.

As Cavin-1 is present in the muscle cells, patients with type 4 have mild muscle weakness and elevated creatine kinase¹⁵.

Life expectancy, mainly in type 2, is substantially decreased, with death not infrequently occurring before the age of 30 years (personal experience based on 20 patients who died in the last 19 years). The causes of death are related to diabetes (renal failure, sudden death), liver (cirrhosis, digestive bleeding) or infections.

Diagnosis and Treatment

The CGL diagnosis is based on clinical data: acromegaloid features, acanthosis nigricans, reduction of total body fat, muscular hypertrophy, and protrusion of the umbilical scar. Also, laboratory data can show diabetes with severe insulin resistance and hypertriglyceridemia. Imaging tests can help identify ectopic deposits of fat mainly in the liver and pancreas (hepatic steatosis with hepatomegaly and pancreatic steatosis). The DXA can confirm the low body fat and high bone density³⁰.

The treatment of CGL consists of strict control of the diet with the decrease of the intake of fat, principally, triglycerides and foods with a high glycemic index to prevent and control comorbidities²⁹. However, the ideal diet is a challenging goal to achieve because of the increased appetite and the severe restriction advocated.

Physical activity should also be encouraged to improve control of comorbidities, except in those patients with contraindications such as severe cardiomyopathy²⁹.

Regarding drug treatment, these patients can be treated with the usual medications for diabetes, hypertension, and dyslipidemia guidelines. The first choice for treatment of diabetes and insulin resistance is metformin, but usually, it is not enough. Unlike the treatment of partial lipodystrophy, thiazolidinediones should be used with caution²⁹. Other oral antidiabetic agents are used, but they were not specifically studied in CGL patients. There are data in animals suggesting that the use of SGLT2 inhibitors (dapagliflozin) could have benefits preventing cardiomyopathy³⁵; studies are needed to confirm this in humans. As the disease progresses and severe insulin resistance occurs, high daily doses of insulin are needed. The lack of subcutaneous adipose tissue is a problem in administering the high doses of insulin. More concentrated insulin (U-300 or U500) may be required³⁶. These patients present severe dyslipidemia, mainly due to the increase of triglycerides and low HDL, and therefore, the use of fibrate is sometimes necessary to prevent acute pancreatitis. In addition, owing to the high cardiovascular risk of these patients, intervention with a statin should be considered, and the targets of LDL or non-HDL should be strict²⁹.

Daily injections of metreleptin cause a significant decrease in appetite and bring benefits by lowering glycemia, triglyceridemia, and liver enzymes. It is notable, especially in children, the reduction of abdominal circumference, probably due to a reduction of hepatomegaly.

Conclusion

CGL is a rare and severe disease that can occur with diabetes (usually requiring high doses of insulin) and early death. The phenotype of the patient is quite characteristic, requiring, however, knowledge of the syndrome by the health professionals to make an early diagnosis. Metreleptin seems to be the only medication at the moment that can modify the natural history of the disease.

Conflict of interest

None.

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