Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Endocrinology

The life of a Patient without Adipose Tissue: From Adipocyte Dysfunction to Metabolic Complications

Sara. IJDDA[1*], Meriem Ben Lafqih[1], Sana. Rafi[1], Ghizlane. El Mghari[1], Nawal. El Ansari[1]

[1]Department of Endocrinology, Diabetology, Metabolic Diseases and Nutrition, University hospital Mohamed VI, Marrakesh, Morocco

DOI: 10.36347/sjmcr.2022.v10i04.016 | **Received:** 13.02.2022 | **Accepted:** 22.03.2022 | **Published:** 16.04.2022

***Corresponding author:** Sara Ijdda
Department of Endocrinology, Diabetology, Metabolic Diseases and Nutrition, University hospital Mohamed VI, Marrakesh, Morocco

Abstract **Case Report**

Life without adipose tissue: Congenital generalized lipodystrophy; Origin, pathophysiology and therapeutic management Congenital Generalized Lipodystrophies also known as Berardinelli-Seip Congenital Lipodystrophy (BSCL) represent the most extreme phenotype of lipodystrophies. BSCLs are characterized by an almost total loss of adipose tissue and a predisposition to develop metabolic complications such as diabetes, hypertriglyceridemia (hyperTG) and non-alcoholic fatty liver disease (NAFLD). Four subtypes of BSCL are distinguished according to the gene involved: AGPAT2 encoding the enzyme 1-acylglycerol-3-phosphate O acyltransferase 2, BSCL2 encoding Seipin, and more rarely CAV1 and PTRF encoding caveolae-associated proteins, respectively Caveolin-1, and Polymerase 1 and Transcription Releasing Factor (also known as Cavin-1). The study of the pathophysiology of BSCL, through clinical work and the generation of relevant animal and cellular models, has made it possible to understand how the absence of these proteins leads to primary and severe adipocyte dysfunction. It also highlights the critical importance of the adipose tissue in carbohydrate-lipid homeostasis, through its role as a storage site for energy molecules and its endocrine action. In this article, we will focus on the clinical features, molecular mechanisms, and treatment of congenital lipodystrophies. BSCL is an extreme phenotype that provides a unique opportunity to study the pathophysiological consequences of life without adipose tissue.

Keywords: Congenital lipodystrophy - lipoatrophy- insulin-resistance- Berardinelli-Seip.

INTRODUCTION

Generalized congenital lipodystrophy (GCL), also known as congenital Berardinelli-Seip lipodystrophy (BSCL), represents the most extreme phenotype of lipodystrophies with the loss of almost all body fat. It is a rare entity with a prevalence of 1/1000000, seen at birth or in the first months of life, predisposing to the early development of metabolic complications such as diabetes, hypertriglyceridemia and fatty liver disease during childhood [1]. This disease was reported in the 1950s in Brazil by Dr. Waldemar Berardinelli [2] and in Norway by Dr Martin Seip [3]. BSCL is a genetic disease inherited in an autosomal recessive fashion. Four genes involved in this disease have been detected: BSCL2, AGPAT2, CAV1, PTRF coding respectively for seipine, AGPAT2, caveolin-1 and cavine1. In this article, we report the case of a patient in who generalized congenital lipodystrophy was revealed by major hypertriglyceridemia.

CASE REPORT

28-year-old patient, eldest of 3 siblings, from a non-consanguineous marriage, who had menarche at the age of 20, with irregular cycles such as spaniomenorrhea. She has diabetic inheritance in maternal grandparents, the mother at the age of 27, the maternal uncle at the age of 36, and the sister with a profile of type 1 diabetes. The diagnosis of diabetes was revealed in our patient by a polyuropolydipsic syndrome with moderate weight loss at the age of 14 years, and then she was put on 2 mixed insulins and a rapid insulin with high doses at a rate of 2.2 IU / kg. At the age of 16, she presented with acute pancreatitis with revelation of major hypertriglyceridemia at 96 mg / l, following which, she was referred to endocrinology for further management. On clinical examination, we found an acromegaloid facies, acanthosis nigricans and adipose tissue atrophy involving the entire body and limbs with an appearance of pseuphlebomegaly. Muscle hypertrophy with clitoral hypertrophy and mild

hirsutism were also revealed. The neurological examination was without abnormalities. Abdominal ultrasound revealed steatotic hepatomegaly with splenomegaly, echocardiography and osteodensimetry were without abnormalities.Unfortunately, and the genetic study was not carried out due to the unavailability of these studies in our context. Therefore, we retained the diagnosis of generalized congenital lipodystrophy probably type 1 on the clinical and imagery arguments.

As for the assessment of complications, we reported bilateral diabetic retinopathy, with proteinuria at 3.18g / 24h, echdoppler of the renal arteries, supraortic arteries and arteries of the lower limbs were without abnormalities as well as the coroscan and pancreatic MRI were normal; while the fibroscann had objectified a fibrosis estimated at F0-F1. Treatment focused on hygiene and dietary measures, taking metformin, the combination of fibrate 160mg and pravastatin 40mg, and a converting enzyme inhibitor for his nephropathy, as well as the adjustment of his insulin doses. Furthermore, the patient now benefits from LDLpheresis sessions every 15 days for life, with a good biological evolution, in this case a triglyceride level between 4 and 5g/l. The sister was summoned to type her diabetes and to find out if she also has lipodystrophic syndrome.

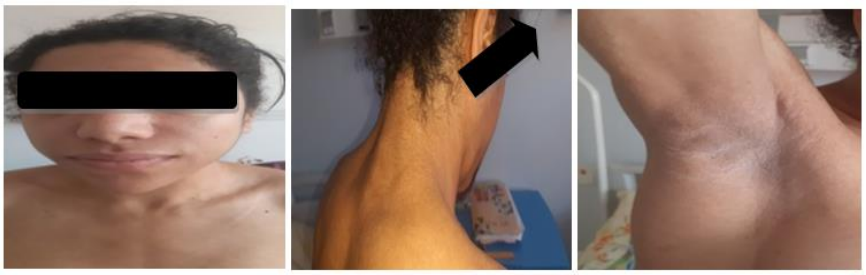

Fig-1 and 2: Acromegaloid facies and acanthosis nigricans

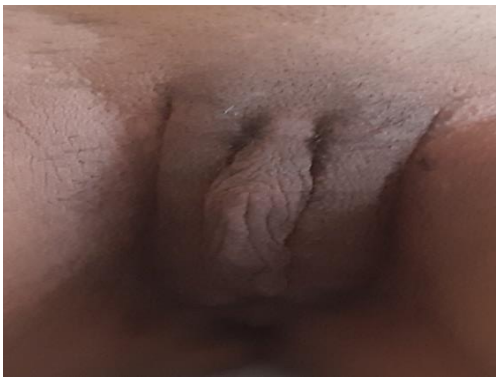

Fig-3: Clitoral hypertrophy

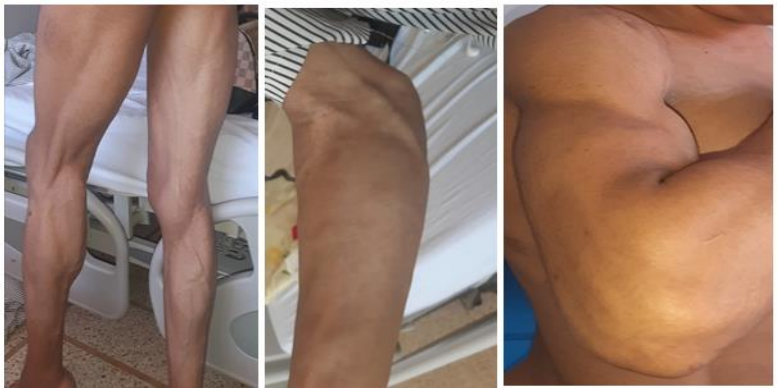

Fig-4, 5 and 6: Pseudophlébomegaly and muscle hypertrophy

DISCUSSION

BSCL is a rare disease inherited in an autosomal recessive fashion. Four subtypes are currently distinguished according to the causative gene involved:

*BSCL1 due to mutations in the gene encoding the enzyme 1-acylglycerol-3-phosphate O-acyltransferase (AGPAT) 2 [4];

*BSCL2 due to mutations in the gene encoding Seipine [5];
*BSCL3 and BSCL4 due to protein mutations associated with caveolae, respectively Caveolin-1 (CAV1) [6] and PTRF (Polymerase 1 and transcription release factor) [7] also called Cavin-1.

The first two subtypes linked to AGPAT2 or to Seipine are by far the most frequent, representing around 95% of the variants; while lipodystrophies linked to Caveolin-1 or Cavin-1 represent a minority of cases.

AGPAT2 is an enzyme of the triglyceride synthesis pathway involved in the synthesis of precursors of several membrane phospholipids, including phosphatidyl-inositol-3kinase (PI3K) involved in the insulin signaling pathway, after its attachment to its receiver. Seipine allows the formation of the lipid droplet from the endoplasmic reticulum thus ensuring initiation, maturation and maintenance.

Generalized lipodystrophy originates from a defect in the differentiation of preadipocytes into adipocytes, or a problem with the maintenance of adipocytes in the mature state leading to cell death. Primary adipocyte dysfunction alters the lipid storage capacities in adipose tissue and the secretion of the two key adipokines, leptin, the satiety hormone, and adiponectin, an insulin-sensitizer adipokine. The decrease in storage capacity will lead to the release of lipids in the form of free fatty acids and triglycerides into the circulation; which will promote the ectopic deposition of lipids in different organs. The consequences are the development of insulin resistance with systemic repercussions. This will lead to an increase in blood sugar levels and promote glucotoxicity which will participate in the development of various diabetic complications [8, 9].

The total absence of adipose tissue is the major characteristic of BSCL; it concerns the whole body and the limbs, the subcutaneous veins are very visible subcutaneously (pseudophlebomegaly) and the prominent muscles due to the lack of fat [1]. Muscle hypertrophy is an important part of the visual diagnosis and is present in most patients with BSCL from birth [1].

BSCL is associated with metabolic complications classically mirrored in obese patients. Historically, BSCL has been named lipoatrophic diabetes due to the presence of severe insulin resistance, both muscular and hepatic [10,11]. Due to insulin resistance, some patients require extremely high doses of insulin for glycemic control (> 2 IU / kg / day). Due to difficulties in achieving adequate blood sugar control, patients with diabetes can quickly develop degenerative complications, such as retinopathy, nephropathy, and neuropathy; like the case of our patient.

A classic consequence of extreme insulin resistance and hyperinsulinemia, acanthosis nigricans, present in the majority of patients with BSCL. Hyperinsulinemia, through its stimulating effect on IGF1 (insulin growth factor1) receptors, is also implicated in organomegaly (liver, spleen, pancreas) often noted in BSCL. Patients develop combined dyslipidemia with first manifestation is severe hypertriglyceridemia (hyperTG) [12, 13]. Hepatic steatosis, classically associated with hyperTG, is often diagnosed in BSCL patients and may be complicated by fibrosis (NASH) and progress to cirrhosis. It can also be noted that certain severe hyperTG (> 20 g / L) can induce acute pancreatitis; like our case, where the acute pancreatitis was indicative of hypertriglyceridemia. As expected, lipoatrophy causes a drastic drop in the plasma concentrations of the two major adipokines, leptin and adiponectin [14, 15]. Severe hypoleptinemia induces chronic overeating, which largely contributes to the worsening of metabolic complications [16].

In terms of cardiovascular complications, hypertrophic cardiomyopathy is often reported in BSCL, and would be more common in patients with mutations in seipine or cavin-1 [3, 17, 18].

An increase in the size of the external genitalia is often reported in patients with BSCL [12, 18, 19]. Mild hirsutism and irregular menstruations are common, and some patients may present with primary amenorrhea. Polycystic ovary syndrome is often observed, probably related to insulin resistance and excessive production of ovarian androgens in these women. Hypoleptinemia causes a loss of the ultradian rhythm of the gonadotropins and therefore anovulation.

Involvement of the nervous system is characterized by mild or moderate intellectual retardation with neurological disturbances such as spasticity or lethal encephalopathy [20, 21].

Bone abnormalities are represented by an acromegaloid appearance, secondary to hypertrophy of bone structures, by long-term activation of IGF receptors by chronic hyperinsulinism [1, 12].

Confirmatory diagnosis is based on genetic study, which is not common practice in our context [22]. Lipodystrophic syndromes are difficult to treat since currently no molecule is able to cause the expansion of adipose tissue in lipoatrophic areas, apart from ongoing research into cell therapy [23]. Currently, treatments are aimed at preventing and / or improving metabolic complications associated with BSCL. Management of insulin resistance is central but often disappointing.

It is important to limit the daily calorie intake in order to control blood sugar and hyperTG. Physical activity is also strongly recommended [24].

Recombinant leptin (metreleptin), effective on associated metabolic disorders but does not improve lipoatrophy. She received European Marketing Authorization on July 30, 2018, in the treatment of metabolic complications associated with leptin deficiency in lipodystrophic patients, from the age of 2 years in GCL when standard treatments have not made it possible to achieve sufficient metabolic control. It is given as a daily subcutaneous injection [24].

Regarding antidiabetic treatments, metformin remains a first-line treatment due to its hepatic insulin-sensitizing action, even if it has no action on the peripheral target tissues of insulin (muscle and adipose tissue) [23].

Glucagonlike peptide-1 (GLP-1) receptor agonists are often useful in treating hyperglycemia and overeating, as well as ultra-concentrated insulin.

Finally, fibrates can be used in case of hypertriglyceridemia> 5g or in combination with statins in case of mixed dyslipidemia.

Genetic screening can be offered to relatives to allow earlier treatment; with genetic counseling for heterozygous parents.

CONCLUSION

Lipodystrophic syndromes are rare diseases, difficult to diagnose, the management of which requires a multidisciplinary approach. However, they represent a model of pathophysiological study that has revealed the importance of the energy storage capacities and endocrine functions of adipose tissue, in the metabolic homeostasis of the whole body. Congenital generalized lipodystrophies are extreme manifestations of adipocyte dysfunction characterized by the almost total absence of white adipose tissue. The clinical manifestations are precocious, variable and severe and, at present, recombinant leptin is the most validated therapeutic option for the improvement of the metabolic complications of BSCL. Cell therapy could offer hope in the longer term, but the proof of preclinical concepts has yet to be done.

REFERENCES

1. Patni, N., & Garg, A. (2015). Congenital generalized lipodystrophies—new insights into metabolic dysfunction. *Nature Reviews Endocrinology*, *11*(9), 522-534.
2. Berardinelli, W. (1954). An undiagnosed endocrinometabolic syndrome: report of 2 cases. *The Journal of Clinical Endocrinology & Metabolism*, *14*(2), 193-204.
3. Seip, M. (1959). Lipodystrophy and gigantism with associated endocrine manifestations; A new diencephalic syndrome?. *Acta Pediat.*, *48*, 555-574.
4. Agarwal, A. K., Arioglu, E., De Almeida, S., Akkoc, N., Taylor, S. I., Bowcock, A. M., ... & Garg, A. (2002). AGPAT2 is mutated in congenital generalized lipodystrophy linked to chromosome 9q34. *Nature genetics*, *31*(1), 21-23.
5. Magré, J., Delépine, M., Khallouf, E., Gedde-Dahl, T., Van Maldergem, L., Sobel, E., ... & BSCL Working Group. (2001). Identification of the gene altered in Berardinelli–Seip congenital lipodystrophy on chromosome 11q13. *Nature genetics*, *28*(4), 365-370.
6. Kim, C. A., Delépine, M., Boutet, E., El Mourabit, H., Le Lay, S., Meier, M., ... & Magré, J. (2008). Association of a homozygous nonsense caveolin-1 mutation with Berardinelli-Seip congenital lipodystrophy. *The Journal of Clinical Endocrinology & Metabolism*, *93*(4), 1129-1134.
7. Hayashi, Y. K., Matsuda, C., Ogawa, M., Goto, K., Tominaga, K., Mitsuhashi, S., ... & Nishino, I. (2009). Human PTRF mutations cause secondary deficiency of caveolins resulting in muscular dystrophy with generalized lipodystrophy. *The Journal of clinical investigation*, *119*(9), 2623-2633.
8. Mann, J. P., & Savage, D. B. (2019). What lipodystrophies teach us about the metabolic syndrome. *The Journal of Clinical Investigation*, *129*(10), 4009-4021.
9. Savage, D. B., Watson, L., Carr, K., Adams, C., Brage, S., Chatterjee, K. K., ... & Sleigh, A. (2019). Accumulation of saturated intramyocellular lipid is associated with insulin resistance [S]. *Journal of lipid research*, *60*(7), 1323-1332.
10. Robert, J. J., Rakotoambinina, B., Cochet, I., Foussier, V., Magre, J., Darmaun, D., ... & Capeau, J. (1993). The development of hyperglycaemia in patients with insulin-resistant generalized lipoatrophic syndromes. *Diabetologia*, *36*(12), 1288-1292.
11. Petersen, K. F., Oral, E. A., Dufour, S., Befroy, D., Ariyan, C., Yu, C., ... & Shulman, G. I. (2002). Leptin reverses insulin resistance and hepatic steatosis in patients with severe lipodystrophy. *The Journal of clinical investigation*, *109*(10), 1345-1350.
12. Seip, M., & Trygstad, O. J. A. P. (1996). Generalized lipodystrophy, congenital and acquired (lipoatrophy). *Acta Paediatrica*, *85*, 2-28.
13. Prieur, X., Le May, C., Magré, J., & Cariou, B. (2014). Congenital lipodystrophies and dyslipidemias. *Current atherosclerosis reports*, *16*(9), 1-11.
14. Haque, W. A., Shimomura, I., Matsuzawa, Y., & Garg, A. (2002). Serum adiponectin and leptin levels in patients with lipodystrophies. *The Journal of Clinical Endocrinology & Metabolism*, *87*(5), 2395-2398.

15. Antuna-Puente, B., Boutet, E., Vigouroux, C., Lascols, O., Slama, L., Caron-Debarle, M., ... & Magre, J. (2010). Higher adiponectin levels in patients with Berardinelli-Seip congenital lipodystrophy due to seipin as compared with 1-acylglycerol-3-phosphate-o-acyltransferase-2 deficiency. *The Journal of Clinical Endocrinology & Metabolism*, *95*(3), 1463-1468.
16. Aotani, D., Ebihara, K., Sawamoto, N., Kusakabe, T., Aizawa-Abe, M., Kataoka, S., ... & Nakao, K. (2012). Functional magnetic resonance imaging analysis of food-related brain activity in patients with lipodystrophy undergoing leptin replacement therapy. *The Journal of Clinical Endocrinology & Metabolism*, *97*(10), 3663-3671.
17. Lupsa, B. C., Sachdev, V., Lungu, A. O., Rosing, D. R., & Gorden, P. (2010). Cardiomyopathy in congenital and acquired generalized lipodystrophy: a clinical assessment. *Medicine*, *89*(4), 245.
18. Van Maldergem, L., Magre, J., Khallouf, T. E., Gedde-Dahl, T., Delepine, M., Trygstad, O., ... & O'Rahilly, S. (2002). Genotype-phenotype relationships in Berardinelli-Seip congenital lipodystrophy. *Journal of medical genetics*, *39*(10), 722-733.
19. Agarwal, A. K., Simha, V., Oral, E. A., Moran, S. A., Gorden, P., O'Rahilly, S., ... & Garg, A. (2003). Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. *The Journal of Clinical Endocrinology & Metabolism*, *88*(10), 4840-4847.
20. Guillén-Navarro, E., Sánchez-Iglesias, S., Domingo-Jiménez, R., Victoria, B., Ruiz-Riquelme, A., Rábano, A., ... & Araújo-Vilar, D. (2013). A new seipin-associated neurodegenerative syndrome. *Journal of medical genetics*, *50*(6), 401-409.
21. Schuster, J., Khan, T. N., Tariq, M., Shaiq, P. A., Mäbert, K., Baig, S. M., & Klar, J. (2014). Exome sequencing circumvents missing clinical data and identifies a BSCL2 mutation in congenital lipodystrophy. *BMC medical genetics*, *15*(1), 1-6.
22. Patni, N., & Garg, A. (2015). Congenital generalized lipodystrophies—new insights into metabolic dysfunction. *Nature Reviews Endocrinology*, *11*(9), 522-534.
23. Brown, R. J., Araujo-Vilar, D., Cheung, P. T., Dunger, D., Garg, A., Jack, M., ... & Yorifuji, T. (2016). The diagnosis and management of lipodystrophy syndromes: a multi-society practice guideline. *The Journal of Clinical Endocrinology & Metabolism*, *101*(12), 4500-4511.
24. Sollier, C., Vatier, C., Capel, E., Lascols, O., Auclair, M., Janmaat, S., ... & Vigouroux, C. (2020, February). Lipodystrophic syndromes: From diagnosis to treatment. In *Annales d'Endocrinologie* (Vol. 81, No. 1, pp. 51-60). Elsevier Masson.