Berardinelli-Seip Congenital Lipodystrophy in a Filipino Child

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ABSTRACT

Berardinelli-Seip Congenital Lipodystrophy (BSCL) is an autosomal recessive inborn error of the common pathway of acylglycerol and phospholipid synthesis. Patients with this condition present with generalized lipoatrophy, hepatomegaly, acromegalic features, hypertrichosis, and developmental delay. But on workup, they may also be discovered to have hypertriglyceridemia with or without hypercholesterolemia and insulin resistance. A high index of suspicion is required for diagnosis which may have implications in management. Here we present a 5-year old male with clinical features of BSCL. BSCL2 gene sequencing done showed a homozygous c.782dupG, p.(Ile262Hisfs*12) sequence alteration, classified as pathogenic, hence, confirming the diagnosis of BSCL. This is the first reported case in the Philippines.

Key Words: Berardinelli-Seip Congenital Lipodsytrophy, insulin resistance

INTRODUCTION

Berardinelli-Seip Congenital Lipodystrophy is a rare disorder of the common pathway of acylglycerol and phospholipid synthesis. It was first reported in Brazil in 1954 by W. Berardinelli and was subsequently confirmed in Norway in 1959 by Martin Seip. It has an estimated prevalence of less than 1 case in 12 million.[1,2,3]

Implicated genes include 1-Acylglycerol-3-Phosphate-O-Acyltransferase 2 (*AGPAT2 or BSCL1*) gene on chromosome 9q34, Berardinelli-Seip Congenital Lipodystrophy 2 (*BSCL2)* gene on chromosome 11q13, and recently, *CAV-1* gene and *PTRF* gene. *AGPAT2* gene encodes lysophosphatidic acid acyltransferase (LPAAT-β), which catalyzes intermediate products of the triglyceride biosynthetic pathway such as phosphatidic acid and diacylglycerol. These serve as intermediates for biosynthesis of glycerophospholipids, which are integral components of all cell membranes. *BSCL2* gene, on the other hand, encodes seipin, an endoplasmic reticulum protein that was proposed to influence adipocyte differentiation and lipid droplet formation. Both caveolin 1 ad PTRF/cavin proteins, encoded by *CAV-1* gene and *PTRF* gene, respectively, are essential for the formation of caveolae in adipocytes. These proteins are involved in a lot of cellular processes such a fatty acid and cholesterol uptake, cholesterol accumulation in lipid droplets, and lipolysis.[4] The pathophysiology of the disorder has now been more understood than it was years ago. Figure 1 shows the molecular mechanisms by which disruption of the 4 genes presented causes BSCL.

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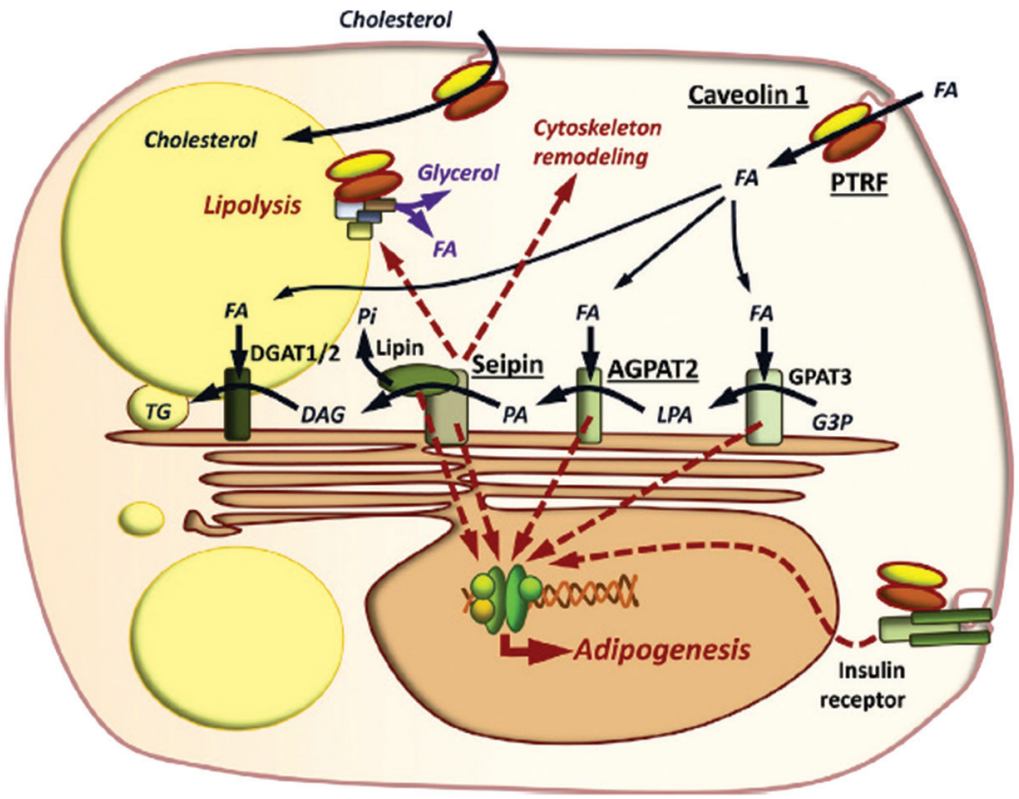

Figure 1. Molecular pathophysiology of BSCL showing the products of the genes implicated in this condition. Disruption of these proteins *(underlined)*, which have multiple roles in adipocyte development and function such as lipolysis, cytoskeleton remodelling and adipogenesis *(red broken arrows)*, cause the manifestations in BSCL.

Adapted from the Mouse Models of Lipodystrophy and Their significance in Understanding Fat Regulation by Justin J. Rochford. Current Topics in Developmental Biology, Volume 109:53-96 (2014).

In a genotype-phenotype correlation study, two main types of this condition were presented primarily based on the gene involved. BSCL type 1, the type with *AGPAT2/BSCL1* mutations, is associated with a milder form of the condition which includes delayed or incomplete presentation of lipoatrophy and low frequency of mental retardation. BSCL type 2, on the other hand, is more associated with mental retardation, early and the generalized onset of lipoatrophy and premature death from heart and liver complications. Another type, which is unlinked to either of the genes discussed, was also mentioned but data is still scarce as there are only a limited number of cases reported.[1,5]

Given the rarity of the condition, the diagnosis may be missed. Patients with BSCL classically present with distinct facial features from generalized lipoatrophy. They also have hepatomegaly, acromegalic features, hypertrichosis, and developmental delay. Careful evaluation, appropriate subspecialty referrals, and work-ups are necessary. Having a confirmed diagnosis allows the anticipation of potential problems and prepares families for possible outcomes. This is the first reported case of Berardinelli-Seip Congenital Lipodystrophy in the Philippines.

CASE PRESENTATION

The patient was a 5-year-old male who initially consulted for abdominal distension. He was the youngest of a sibship of three born to a healthy non-consanguineous couple of Filipino descent. He had an unremarkable neonatal course and there was no note of dysmorphic features. At 3 months of age, he had jaundice and abdominal enlargement. An abdominal ultrasound showed normal results. He subsequently had hypertrophied muscles on the upper extremities and lower extremities, excessive facial and body hair. The family decided to seek to consult and he was first seen in our clinic at 5 years of age. A review of his developmental history showed delays in all domains of development.

On physical examination, he had generalized lipoatrophy (Figure 2) most prominent on the face, trunk, and limbs; acromegalic features exemplified by prominent orbital ridges, enlarged hands and feet; and enlarged external genitalia. His abdomen was protuberant, with hepatomegaly 8 cm below the right costal margin. He had marked acanthosis nigricans on the neck, axillae and groin and hypertrichosis, manifested as the low frontal hairline and excessive hair on

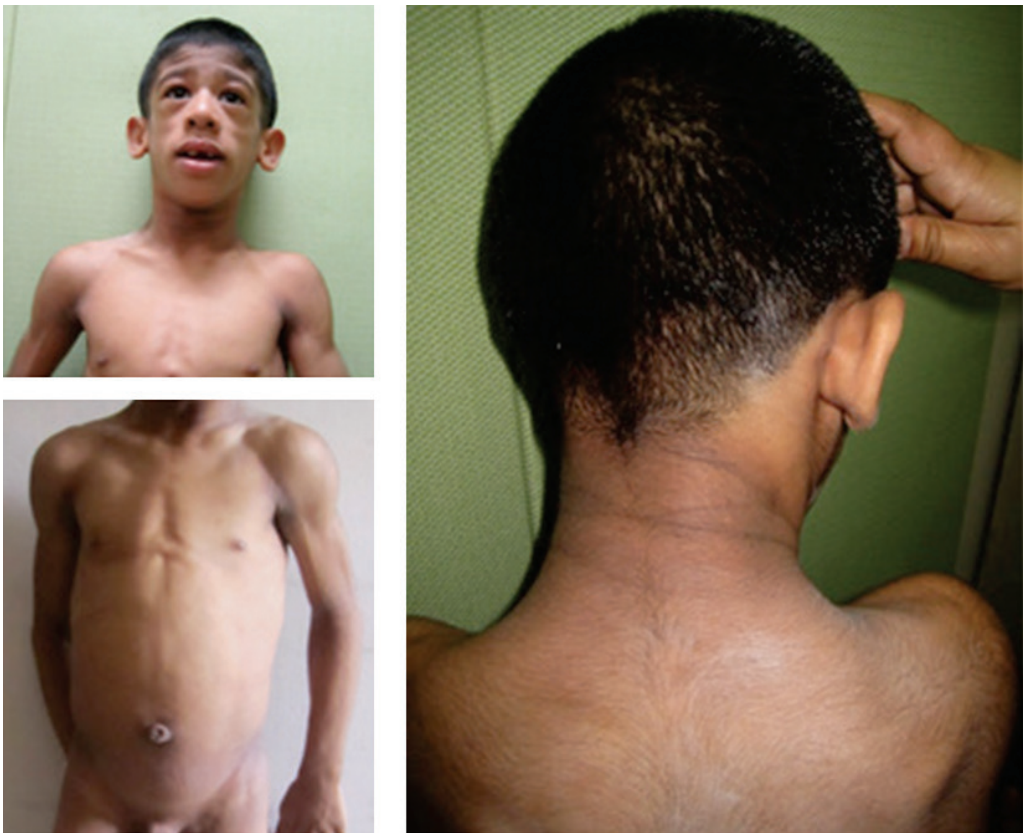

Figure 2. Patient showing features of Berardinelli-Seip Congenital Lipodystrophy such as generalized lipoatrophy, acanthosis nigricans and hypertrichosis.

both upper and lower extremities. Veins were also prominent in both the upper and lower extremities.

Abdominal ultrasonography showed fatty liver changes, morphologically intact kidneys but enlarged for age, and normal ultrasound of the spleen and pancreas. Total cholesterol, triglycerides, and LDL cholesterol levels were elevated at 200.38 mg/dL (reference value: < 200 mg/dL), 114.73 mg/dL (reference value: ≤ 100 mg/dL) and 135.77 mg/dL (reference value: ≤ 130 mg/dL), respectively. HDL cholesterol is normal at 41.81 mg/dL (reference value: > 40.0-60.0 mg/dL). On repeat 1 year after management was started, HDL cholesterol is already low at 34.36 mg/dL (reference value: 40.0-60.0 mg/dL) while LDL cholesterol is high at 135.14 mg/dL (reference value: ≤ 130 mg/dL). Total cholesterol is already acceptable for age while triglycerides even increased to 130.09 mg/dL (reference value: ≤ 100 mg/dL). Alanine transaminase was 115 U/L (reference value: 0-30U/L), aspartate transaminase was 59 U/L (reference value: 0-34U/L), and alkaline phosphatase was 199 umol/L (36-92 umol/L). Ophthalmologic evaluation done to check for findings of complications for hyperlipidemia and diabetes was unremarkable. Echocardiography showed a concentric left ventricular hypertrophy without a significant outflow obstruction. Hemoglobin A1c (HbA1c) was normal at 5.4% (reference value: <6.5%).

The patient's nutritional status was based on the WHO Child Growth Standard Weight-for-age, height-for-age, and BMI-for-age. Dietary intake was evaluated in the form of a three-day food analysis using the Philippines Food Exchange List (FEL) and Philippine Food Composition Table (PhilFCT). Results revealed an estimated total caloric intake of 3,730 calories, which is 248% in terms of adequacy based on the recommended nutrient intake per day for a 5-year old child. Looking at the macronutrient intake and analyzing it based on Recommended Energy and Nutrient Intake (RENI) for 5-year-old male, intake of carbohydrates exceeds average requirement by 206% for carbohydrates (463.72g), 510% for protein (112.32g) and 381% for fats (160.28g), as a result of hyperphagia. Micronutrient analysis of intake shows overly high percent adequacy for all of the micronutrients most especially for phosphorus (1577.54mg) and iron (22.73mg). Further assessment during the interview denotes a lack of knowledge on proper food choices in the management of the condition.

His development profile was evaluated based on the interview with his father and mother, clinical observations and examination. The Battelle Developmental Inventory (Second Edition) was likewise administered at the chronological age of 5 years and 3 months, showing delays in all domains of development, most especially in his communication and

cognitive skills (Table 1). The Vineland Adaptive Behavior Scales, Second Edition was also used to measure his personal and social skills needed for daily living, administered at a chronological age of 5 years and 3 months (Table 2), which showed a low adaptive level with mild to moderate deficits. His developmental assessment shows delays in all domains of development, consistent with a mild intellectual disability.

Table 1. Results of the Battelle Developmental Inventory (Second Edition) administered to the patient at chronological age 5 years and 3 months

Domains and Subdomains	Age equivalent	Developmental quotient
Adaptive		58
Self-Care	3 years	
Personal Responsibility	2 years, 7 months	
Personal-Social		55
Adult Interaction	1 year, 2 months	
Peer Interaction	<2 years	
Self-Concept and Social Role	2 years	
Communication		55
Receptive Communication	11 months	
Expressive Communication	8 months	
Motor		55
Gross Motor	2 years, 3 months	
Fine Motor	2 years, 1 month	
Perceptual Motor	<2 years	
Cognitive		55
Attention and Memory	1 year, 3 months	
Reasoning and Academic Skills	<2 years	
Perception and Concepts	1 year, 3 months	
Total		48

BSCL2 gene sequencing done showed a homozygous c.782dupG, p.(Ile262Hisfs*12) sequence alteration, classified as pathogenic, hence, confirming the diagnosis of Berardinelli-Seip congenital lipodystrophy.

A multidisciplinary approach to management was done. The family underwent pre-test and post-test genetic counseling. Once the diagnosis was confirmed, complications, prognosis, and course of management were explained**.** At the pre-test and post-test counseling, the parents were already positive and relieved. It was shared that at first, they thought that the condition of their son was just a simple case of developmental delay. For some time, they were at a loss because their son was subjected to a series of laboratory tests and went through different check-ups. When he was diagnosed with Berardinelli-Seip Congenital Lipodystrophy, it was when they started to understand the condition better. With the confirmation of the condition through genetic testing, they were able to understand the possible symptoms, complications, and outcomes.

Monthly follow-up was suggested to monitor and evaluate compliance to the dietary management. The patient has started both dietary management and developmental/behavioral therapies.

DISCUSSION

The clinical diagnosis of BSCL is established by the presence of 3 major criteria or 2 major criteria plus 2 or more minor criteria. For the patient, all 5 major criteria were present namely: lipoatrophy affecting the trunk, limbs, and face, acromegalic features, hepatomegaly, elevated serum triglycerides with hypercholesterolemia, and insulin resistance. Also, minor criteria such as intellectual

Table 2. Results of the Vineland Adaptive Behavior Scales, Second Edition administered to the patient at chronological age 5 years and 3 months

Subdomain / Domain	Raw score	Standard score	Adaptive level	Age equivalent
Receptive	7		Low	8 months
Expressive	17		Low	10 months
Written	0		Low	1 year, 10 months
Communication		**42**	**Low**	
Personal	32		Low	2 years, 6 months
Domestic	3		Moderately Low	1 year, 6 months
Community	6		Low	2 years, 2 months
Daily Living Skills		**58**	**Low**	
Interpersonal Relationships	24		Low	11 months
Play and Leisure Time	13		Low	3 months
Coping Skills	4		Low	4 months
Socialization		**55**	**Low**	
Gross	52		Low	2 years
Fine	18		Low	1 year, 6 months
Motor Skills		**56**	**Low**	
Adaptive behavior composite		**51**	**Low with mild to moderate deficits**	

impairment, hypertrichosis, and phlebomegaly, are present. Other minor criteria included are hypertrophic cardiomyopathy, precocious puberty in females, and the presence of bone cysts.[1] This is the reason why abdominal ultrasound, lipid profile, liver function tests, and 2d echocardiography were done. HbA1c, on the other hand, was done to check if the patient already has diabetes mellitus. These diagnostics will also comprise the surveillance for BSCL.[1]

The generalized near-total lack of adiposity in BSCL can be partially explained by both genes implicated in this condition. *AGPAT2* gene, also known as *BSCL1* gene, catalyzes the formation of phosphatidic acid, which is an intracellular signaling molecule important for the normal adipocyte function and has a role in the triacylglycerol synthesis in adipose tissues. Seipin, the protein encoded by *BSCL2*, is postulated to influence the differentiation of adipocytes and the formation of lipid droplets. Metabolically active adipose tissues located in the bone marrow, subcutaneous, intra-abdominal, inter-muscular, and intra-thoracic regions are markedly reduced in both *AGPAT2* and *BSCL2* gene mutations. On the other hand, mechanically important adipose tissues, in areas like the scalp, periarticular, soles, palms, and orbital regions, are reduced in *BSCL2* mutations but not in *AGPAT2* mutations.[3]

Acromegaloid features in BSCL is exemplified by the presence of gigantism, advanced bone age, prognathism, prominent orbital ridges, enlarged hands and feet, clitoromegaly, and enlarged external genitalia in males. These features were attributed to insulin-like growth factor (IGF) hypersecretion. IGF circulates in the blood bound to IGF-binding proteins and interacts with specific receptors on target tissues like bones, to stimulate growth.[6,7] In our patient, these acromegalic features were noted.

Acanthosis nigricans, which is virtually present in all patients with BSCL, is closely associated with insulin resistance. Insulin acts on fibroblasts and keratinocytes. Hence, an increase in insulin concentration leads to an increase in the metabolism, growth, and proliferation of the cells of the epidermis, manifesting as acanthosis nigricans. This appears in the nape, armpit, neck and other flexural areas, as in our patient.[7]

Molecular confirmation may also be done for patients by the identification of biallelic pathogenic variants in one of the two genes implicated in this disorder. Also, a molecular diagnosis may help in prognostication. Our patient, based on the gene involved, BSCL2 gene, is associated with premature death and complications like cardiac and liver failure. Hence, the molecular diagnosis prompted appropriate genetic counseling and prognostication in our patient.

The importance of genetic counseling cannot be overemphasized. It is an autosomal recessive disorder, rendering a 25 % risk of recurrence to siblings of the proband. A discussion of the prognosis and complications of the disorder needs to be done. Surveillance for diabetes mellitus and its complications, hepatic steatosis and cirrhosis, and cardiomyopathy should be performed periodically.[3] The prognosis of patients with BSCL is poor, decreasing the life span to more or less 30 years. The common cause of death is either due to liver disease or infection.[5,8] These things should be discussed.

The initial evaluation of the patient with BSCL requires a multidisciplinary approach. Dietary management, through restriction of fat intake, is pivotal and usually sufficient to maintain normal levels of triglycerides.[1] Diet is considered fundamental in the management of BSCL as complications are highly diet-related. Given the predisposition of patients to dyslipidemia, diabetes and cardiovascular diseases, nutrition therapy focuses on the management of lipid levels, control of blood sugar and management of hyperphagia. Hence, the involvement of a dietician and an endocrinologist in the care for patients with BSCL is critical. Most studies recommend normal distribution of 50-60% carbohydrates, 15-20% protein and 25-30% fat with an energy-restricted diet for adolescents and adults.[9]

Diet has been fundamental in the management of BSCL. Nutrition intervention was focused on the management of lipodystrophy by providing a low fat, low cholesterol diet seconded by modification of carbohydrate sources (complex carbohydrates with low glycemic index) to help regulate blood sugar levels in consideration to insulin resistance. A nutrition care plan was provided to the patient's parents regulation with appropriate monitoring and evaluation measures. For our patient, dietary prescription provided 1700 calories from his usual 3740 calories per day. The strategy is to provide adequate calories to retain weight yet reduce the synthesis of lipids. Macronutrients are provided in 65-20-15 percentage. A low-fat diet of 15% is recommended to regulate satiety, promote efficient metabolism and most importantly, manage dyslipidemia (recommended in the form of monounsaturated fats and long–chain omega-3 fatty acids). Protein allowance was 20% and carbohydrates were increased to 65% but were given the strict emphasis on the selection of food sources with low glycemic index and/or complex carbohydrates, for adequacy. A strategy in addressing hyperphagia is to do small frequent feedings of up to six meals per day with high fiber food choices to provide satiety which will also regulate cholesterol, lipid and sugar levels. Given the active lifestyle of the child, an exercise regimen is at the least priority Nutrition counseling was done and aimed to further emphasize the importance of proper diet, improving food choices and provision of a well- balanced meal, inadequate amounts and small frequent servings to manage the condition.

Evaluation of intervention was done during a follow-up consultation with the dietitian. A diet review was collected to assess intake after the nutrition intervention and there was a 55% change in the patient's caloric intake. Protein intake decreased up to 160% but is still above RENI values appropriate for age. Carbohydrate and fat intake are still elevated at 378.7g and 128.9g but in decreased amount

compared to the initial diet evaluation. Plans on the provision of small frequent feeds (6-7 meals per day) were properly observed, amount of food serving was given more attention and improvement on food choices was given good adherence based on the qualitative evaluation of diet. Based on published reports, diet modification, in the long run may help improve triglyceride level, carbohydrate tolerance, hepatomegaly, and insulin resistance.[3,7,10]

Developmental and behavioral evaluation and management are also crucial in improving the patient's well-being and may also help in compliance with treatment. The patient was started on occupational therapy to develop his fine motor and self-help skills, to start behavior modification techniques, and to improve his focus and attention, compliance, and impulse and frustration control. Speech therapy was likewise started for vocabulary building and to improve his articulation and comprehension. He was also enrolled in Special Education to improve his pre-academic skills and for socialization. This shows that the role of developmental pediatricians and allied medical professionals like occupational therapists, speech therapists, and child psychologists will also be very crucial in the care of our patient.

CONCLUSION

Having a diagnosis of conditions like BSCL allows the anticipation of potential problems and prepares families for possible outcomes. As in this case, the molecular diagnosis did not only confirm BSCL, but also gave the prognostication. BSCL is a condition with multi-systemic involvement which warrants a multidisciplinary approach in management. Specifically, diet plays a significant role in the management of this condition.

Consent

Written informed consent was obtained from the parent of the patient for publication of this case report and the accompanying images.

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Statement of Authorship

All authors participated in the writing of the case report and approved the final version submitted.

Author Disclosure

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