Cardiometabolic Abnormalities in Patients with Berardinelli-Seip Syndrome

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Abstract

Background: Berardinelli-Seip syndrome (BSS) or Generalized Congenital Lipodystrophy often affects the cardiovascular system and also promotes metabolic abnormalities involving glycidic and lipid metabolisms.

Objective: To assess the prevalence of cardiometabolic abnormalities in patients with BSS.

Methods: Twenty-two patients from the state of Rio Grande do Norte, Brazil, diagnosed with BSS, underwent clinical evaluation, resting electrocardiogram, echodopplercardiogram, chest X-ray, 24-hour ambulatory electrocardiogram monitoring, exercise testing and laboratory analysis.

Results: The patients were predominantly young adults, most of whom women. The whole sample showed insulin resistance, *acanthosis nigricans* and diminished HDL-cholesterol. The presence of splenomegaly, hepatomegaly, type II diabetes and elevated triglycerides was constant. Metabolic syndrome was characterized in most patients, which were predominantly women and with a high degree of paternal consanguinity. SAH and prehypertension blood pressure were found in more than half of the patients (77.3%). The echodopplercardiogram showed the presence of CLVH (50%), eccentric left ventricular hypertrophy (4.5%), and normal left ventricular geometry (45.5%). High arrhythmia rates were observed by Holter monitoring, such as ventricular ectopic beats, supraventricular ectopic beats and sustained supraventricular tachycardia. Chronotropic incompetence (54.5%) was observed during exercise testing.

Conclusion: A high prevalence of cardiovascular and metabolic abnormalities was observed in young asymptomatic individuals with BSS. These findings point to the need for systematic cardiological follow-up and of preventive measures in this high-risk group. (Arq Bras Cardiol 2010; 94(1) : 102-110)

Key Words: Lipodystrophy, Congenital Generalized; Metabolism / Genetics; Cardiovascular Diseases / Genetics; Lipid Metabolism / Genetics.

Introduction

BSS or generalized congenital lipodystrophy was described for the first time in Brazil by Berardinelli et al. in 1954[1], in two children[1]. In 1959 Seip et al[2], described this same syndrome in three other patients[2]. BSS has a genetic character with recessive autosomal transmission, and often paternal consanguinity of indeterminate cause, due to mutation in AGPAT2 and Gng3lg[3]. Two loci are described: BSCL1 and BSCL2 in BSS, in chromosomes 9q34 and 11q13, respectively[3]. In a study carried out with 21 patients from Rio Grande do Norte, Brazil, mutation was found in the Gng3lg of 19 individuals and in the AGPAT2[4] of two subjects.

BSS is rare syndrome, with a prevalence of one case per ten million people[3] . The individuals affected present with nonketotic, insulant-resistant type II diabetes, accompanied by the almost total absence of subcutaneous adipose tissue. Diagnosis can be established at birth or during childhood and is characterized by clinical, metabolic and laboratory alterations which include the following: absence or decrease of subcutaneous fat tissue; accelerated growth with acromegaloid pattern; and accentuated somatic and skeletal development. The presence of hepatomegaly is common, owing to fat infiltration that may evolve to cirrhosis, splenomegaly, acanthosis nigricans, macroglossia, gynecomastia, hyperglycemia hypertriglyceridemia, hyperinsulinemia, decreased levels of HDL-cholesterol (HDL-c); sometimes accompanied by elevated total cholesterol (C-t) and LDL-cholesterol (LDL-c). The serum levels of leptin and adiponectin are extremely low[3,5,6].

There are few published articles on cardiac alterations as a consequence of BSS. There are fewer than twenty reports on cardiac alterations, with sample size not exceeding 10 patients[7-14]. These studies showed that the most frequent cardiovascular alterations were cardiac hypertrophy; cardiomegaly and hypertrophic cardiomyopaty; particularly

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asymetric septal hypertrophy; left ventricular dysfunction; and systemic arterial hypertension (SAH)[7-17]. There is only one case report in Brazil in which cardiac alterations were described[14].

The objective of this study was to determine cardiovascular and metabolic abnormalities in patients with BSS, using clinical evaluation, biochemical tests, resting electrocardiogram (ECG), chest X-ray, exercise testing, echodopplercardiogram and 24-hour ambulatory ECG monitoring (Holter).

Methods

Subjects

In total, 22 patients with BSS from the state of Rio Grande do Norte, Brazil, were treated at the Endocrinology, Metabology and Cardiology outpatient facility of Onofre Lopes University Hospital (HUOL) at the Universidade Federal do Rio Grande do Norte (UFRN). Each patient or their legal representative signed the free informed consent , which was previously approved by the Institution's Research Ethics Committee (Protocol no. 42/2003). All examinations were conducted on the same day and none of the patients had taken any medication for at least 5 days.

Clinical parameters – A protocol for each patient was filled out, containing personal data, anamnesis and general clinical examination, endocrinological and cardiovascular findings. All examinations were performed by specialized physicians.

Anthropometric assessment – Weight was measured three times on a digital scale (Balmark, São Paulo, SP, Brazil), with a maximum capacity of 160 kg and accurate to 100 g. Waist circunference (WC) was measured on an imaginary horizontal line that passed through the middle point between the lower edge of the last rib and the iliac crest. Body surface area (BSA) was calculated by the DuBois and DuBois equation[18]. Measures of weight and height were used to calculate body mass index (BMI). Children with BMI > 95 percentile were considered obese and those with BMI between percentiles 85 and 95 as overweight[19] . For the adults, BMI was considered normal when it was between 18.5- and 24.9 kg/m^2; overweight between 25.0 and 29.9 kg/m^2 and obese >30 kg/m^2 [20].

Biochemical parameters – Five mL of total blood was collected after a 12h fast. Fasting glucose, C-t, HDL-c and triglycerides (TG) were assessed. Low-density lipoprotein cholesterol (LDL-c) was not calculated because it becomes progressively less accurate with increasing serum TG concentrations and is not used for metabolic syndrome (MS) criteria[20]. The dosages were determined in a biochemical analyzer (Chem Well, Palm City, FL, USA) using specific reagents (Labtest, Minas Gerais, Brasil).

Criteria and guidelines – Normality criteria, defined by the I Guidelines for the Prevention of Atherosclerosis in Childhood[19], by the IV Guidelines for the Prevention of Atherosclerosis of the Brazilian Cardiology Society[20] and by the Brazilian Consensus on Diabetes[21], were adopted. Information on the insulin resistance of each individual was obtained from HUOL patient records.

To assess MS criteria in adolescents and children, NCEP/ATP III[22] norms were adopted, modified for age and requiring the presence of at least 3 of 5 parameters as follows: TG levels ≥ 110 mg/dL; HDL-c ≤ 40 mg/dL; WC ≥ 90 percentile according to sex and age; glycemia ≥ 110 mg/dL; and systolic or diastolic blood pressure (SBP or DBP) ≥ 90 percentile according to sex, age and height. On the other hand, according to NCEP/ATP III[23], for adults MS represents the combination of at least three of the following components: abdominal obesity using WC (men > 102 cm and women > 88 cm); TG ≥150 mg/dL: HDL-c for men < 40 mg/dL and for women < 50 mg/dL; arterial blood pressure ≥ 130 mmHg or ≥ 85 mmHg; and fasting glucose ≥ 110 mg/dL. The presence of type II diabetes mellitus does not rule out the diagnosis of MS. Owing to its simplicity and practicality, this is the definition recommended by the I Brazilian Guidelines for the Diagnosis and Treatment of Metabolic Syndrome[24].

Hemodynamic parameters - Arterial blood pressure (ABP) was measured by the indirect method, using a blood pressure monitor (Welch Allyn, Skaneateles Falls, NY, USA), graduated and calibrated from zero to 300 mmHg. Three measures were taken after a five-minute rest period with the patient in the sitting position. The measuring procedures and arterial pressure classification were conducted according to The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High blood Pressure[25,26]. The ABP values were not rounded off for digits ending in five or zero.

Electrocardiogram - The ECG, performed after a 10-minute rest period, was recorded on an electrocardiographic recording system (Cardioline Delta Plus, Cavareno, Trento, Italy) with 12 derivations. The graphic record was standardized at a velocity of 25mm/s and the device was calibrated with an amplitude of 1 mV, corresponding to 10 mm on the vertical axis[27]. Final assessment was carried out by two cardiologists; since there was a disagreement between the two results, a third professional determined the final result of the examination.

Chest X-ray– The chest X-ray was taken by a device (Emic, Modelo MKTE 500, São Paulo, SP-Brasil) equipped with an Agfa Cr 75.0 (Mortsel-Belgium) digital processing system at maximum inspiration. For the children that were unable to maintain maximum inspiration, the examination was performed at a distance of 1 m, generally in the anterior-posterior projection. In the adults the distance was between 1.75 and 2 m in anterior-posterior projection and left profile. Using this technique, we assessed the cardiac area according to the cardiothoracic index and the pleuropulmonary evaluation, as well as the diaphragm dome[28].

Echodopplercardiogram – This examination was uni- and bidimensional with pulsed and continuous Doppler using color flow imaging (Hewlett Packard, Model 2410 A-Ultrasound System, Andover-MA, USA). Five measures were taken for each variable studied and the mean final value was considered for analysis. The device contained 2.5 and 5.0 mHz transductors that enabled M-mode and bidimensional assessment with pulsed and continuous Doppler. The images and cardiac dimensions were obtained according to American Society of Echocardiography (ASE) recommendations[29,30], from conventional echocardiographic cuts.

To calculate left ventricular mass (LVM), the formula recommended by the ASE and corrected by the Penn convention[31] was adopted. The left ventricular mass index (LVMI) was calculated by correcting the value of mass (g) by BSA (m^2). An LVMI less than or equal to 95 g/m^2 and 115g/m^2 was considered normal for women and men, respectively[32]. The calculation of relative wall thickness (RWT) was obtained by the following formula:

RWT = (2 x PWTd) / LVId

Where PWTd and LVId are posterior wall thickness at the end of diastole and left ventricular end diastolic dimension, respectively.

The patients were classified into four groups of cardiac geometry[32]:

a) Normal geometry = normal LVMI and RWT ≤ 0.42;

b) Concentric remodeling = normal LVMI and RWT > 0.42;

c) Concentric hypertrophy = increased LVMI and RWT > 0.42;

d) Eccentric hypertrophy = increased LVMI and RWT ≤ 0.42.

The ejection fraction (EF) was calculated by Simpson's method from an apical four-chamber view [32]. Values ≥ 55% were considered normal.

Assessment of intracardiac flow patterns followed the guidelines of the Canadian Consensus and served to evaluate LV diastolic function[33]. The following variables were obtained:

a) Peak mitral E-wave velocity (m/s);

b) Peak mitral A-wave velocity (m/s);

c) E/A ratio;

d) Mitral Deceleration Time in m/s corresponding to the time interval between the E-wave peak and its extrapolation to baseline;

e) Left Ventricular Isovolumic Relaxation Time (IVRT) in m/s, corresponding to the interval from aortic valve closure to mitral valve opening.

The first three variables were obtained before and during the strain phase of the Valsalva maneuver.

24-hour ambulatory electrocardiogram monitoring (Holter) – The patients were monitored for 24 hours, using a 3-channel digital recorder (Cardioflash Digital Cardios, São Paulo-SP, Brazil). Preparation, the examination, analysis and the report followed ACC/AHA Guidelines for Ambulatory Eletrocardiography[34].

Exercise testing – was carried out on a treadmill (IMBRAMED, Model Soft Move I, Porto Alegre-RS, Brazil). The patients were prepared for continuous EGG monitoring, using the modified derivations of Mason et al[35]. The examination was initiated using the Bruce protocol[36]. The examination, aimed at assessing clinical, electrocardiographic and hemodynamic responses, and thus followed guidelines for reliable, reproducible and measurable results contained in the II Directive of the Brazilian Society of Cardiology on the Ergometric Test[37].

Statistical analysis – The comparison between the two subgroups was analyzed by the Mann-Whitney test for numerical data and by Fisher's exact test for categorical data (qualitative). The numerical data were summarized and expressed as mean and standard deviation, and the qualitative data as frequency (n) and percentage (%). The Mann-Whitney nonparametric test was used, since the variables did not show normal distribution (Gaussian), owing to the lack of distribution symmetry and mainly because of the small sample size in the subgroups studied. The significance level was set at 5%. Statistical analysis was processed by SAS software 6.04 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

Subjects

The clinical characteristics of the 22 patients studied are shown in figure 1 and table1.

Clinical parameters

Table 1 also describes the clinical parameters. A family history of BSS was identified in 86.4% of the patients, with a predominance in women (92.9%) because of their greater number. Type II diabetes mellitus occurred in 68.2% of the patients, 62.5% of which were men. Insulin resistance and *acanthosis nigricans* was diagnosed in all the patients. MS

Figure 1 - Patients with the Berardinelli-Seip Syndrome

occurred in 81.8% of the cases, with a similar prevalence between genders. Hepatomegaly occurred in 90.9% of the patients, with no difference between genders, and splenomegaly in 45.5%, with a predominance in women.

Antropometric assessment

The anthropometric characteristics of the 22 patients studied are shown in table 1. Mean age was 22.4 ± 9.7 years, with no statistical difference between genders. Mean weight was 56.6 ± 15.1 kg and higher in the men (p=0.003). BMI showed a mean of 21.6 ± 3.3, also higher in the men (p=0.001). Mean BSA was 1.58 ± 0.27 and more elevated in the men (p=0.004). WC showed a mean of 82 ± 9.2, and was significantly higher in the men (p=0.011).

Biochemical parameters

Fasting glucose remained high (177.8 ± 84.4, with no significant difference between genders. Mean C-t was 175.4 ± 38.1, also with no significant difference between genders. Mean HDL-c was 27.4 ± 7.7, and higher in the women (p=0.033). The TGs remained high (331.7 ± 286.4), although with no significant difference between genders (table 1).

Table 1 – Clinical, anthropometric, laboratory and hemodynamic variables in 22 patients with Berardinelli-Seip syndrome according to gender.

Variable	Total	Males	Females	*p*-value
	(n = 22)	(n = 8)	(n = 14)	
Clinical	**n (%)**	**n (%)**	**n (%)**	
Family history	19 (86.4)	6 (75)	13 (92.9)	*
Diabetes mellitus	15 (68.2)	5 (62.5)	10 (71.4)	0.51
Insulin resistance	22 (100)	8 (100)	14 (100)	*
Metabolic syndrome	18 (81.8)	7 (87.5)	11 (78.6)	*
Hepatomegaly	20 (90.9)	7 (87.5)	13 (92.9)	*
Splenomegaly	10 (45.5)	2 (25)	8 (57.1)	0.15
Anthropometric	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	
Age(years)	22.4 ± 9.7	25.8 ± 9.6	20.5 ± 9.6	0.18
Body mass index (Kg/m^2)	21.6 ± 3.3	24.5 ± 2.5	20.0 ± 2.5	0.001
Body surface area (m^2)	1.58 ± 0.27	1.78 ± 0.18	1.46 ± 0.24	0.004
Waist circumference (cm)	82.0 ± 9.2	88.5 ± 8.1	78.2 ± 7.7	0.011
Biochemical				
Fasting glucose (mg/dl)	177.8 ±84.4	182.5 ± 87.7	175.1 ± 85.7	0.91
Cholesterol (mg/dl)	175.4 ± 38.1	167.9 ± 21.3	179.7 ± 45.2	0.99
HDL-c (mg/dl)	27.4 ± 7.7	23.4 ± 5.7	29.7 ± 7.9	0.033
Triglycerides (mg/dl)	331.7 ± 286.4	398.6 ± 270.9	293.4 ± 297.8	0.27
Hemodynamic				
SBP (mmHg)	130.9 ± 23.7	131.3 ± 21.7	130.7 ± 25.6	0.80
DBP (mmHg)	85.5 ± 18.2	82.5 ± 17.5	87.1 ± 19.0	0.57
	n (%)	**n (%)**	**n (%)**	**n (%)**
Normal blood pressure	5 (22.70)	3 (37.5)	2 (14.3)	*
SAH	11 (50)	4 (50)	7 (50)	0.36
Prehypertension	6 (27.3)	1 (12.5)	5 (35.7)	*

*Values are expressed in mean± SD; HDL-c: high-density lipoprotein cholesterol; SBP: systolic blood pressure; DBP: dyastolic blood pressure; SAH: systemic arterial hypertension; *Few cases: <5 patients present or absent*

Arterial blood pressure

Basal heart rate, with a mean of 91.6 ± 8.3, was higher in the women (p=036). SAH occurred in 50% and prehypertension in 27.3% of BSS patients (table 1). The means of SBP and DBP were higher in both genders, although not statistically different.

Basal electrocardiogram

All the patients with BSS showed sinus rhythm; 18.2% had left ventricular hypertrophy (LVH) and 3.6% had alterations in ventricular repolarization. Other alterations were irrelevant (data not shown).

Chest X-ray

Of the 22 patients with BSS, 95.5% had normal chest X-ray. Only one woman showed an increased heart area and pulmonary flow inversion to the apexes (data not shown).

Echodopplercardiogram

Table 2 shows that the echodopplercardiogram was normal in 40.9% of the patients, with no statistical significance between genders. Mild mitral regurgitation appeared in 27.3% of the BSS patients, predominantly in women. Calcification of the aortic valve was diagnosed in 9.1% of the patients and mild aortic regurgitation in 4.5%, all of whom were women. Concentric left ventricular hypertrophy (CLVH) was found in around 50% of the patients from both genders and eccentric left ventricular hypertrophy in 4.5% (predominantly women). Normal left ventricular geometry was present in 45.5% of the cases studied, practically equal in men and women. The patterns of left ventricular diastolic function assessed by transmitral flow were within normal limits, before and during the strain phase of the Valsalva maneuver (table 2). Left ventricular systolic function was assessed by ejection fraction (Simpson), which had a mean value of 67.3%, with no difference between genders.

Table 3 relates the frequency and percentage of LVH in the electrocardiogram and clinical parameters to the echodopplercardiogram (normal or abnormal). LVH in the ECG (30.8%), diabetes mellitus (76.9%), hepatomegaly (100%), splenomegaly (61.5%), and SAH plus prehypertension (92.3%) were more present in the abnormal echodopplercardiogram.

Table 4 relates the frequency and percentage of various clinical parameters and LVH in the electrocardiogram to CLVH in the echocardiogram. Among the eletrocardiographic parameters, 36.4% of LVH was detected only in the presence of CLVH. The most frequent clinical parameters, such as diabetes mellitus (72.7%), hepatomegaly (100%), splenomegaly (63.6%), and SAH plus prehypertension (90.9%) were more observed in the presence of CLVH than in its absence.

24-hour ambulatory electrocardiogram monitoring (Holter)

Table 5 shows the association between arrhythmias determined by Holter and chronotropic incompetence found in exercise testing (ET) compared to CLVH observed on the echocardiogram of 22 patients with BSS. Patients with normal Holter had CLVH present (18.2%) and absent (36.4%), with no significance between the two groups. Ventricular ectopic beats were equally detected in 54.6% of patients with CLVH present and absent. Patients with supraventicular ectopic beats had a percentage of 81.8% associated to CLVH present and 54.6% to CLVH absent. Sustained supraventricular tachycardia was detected in 27.3% of the patients with CLVH present and 9.1% with CLVH absent.

Exercise testing

Chronotropic incompetence was observed in ET in 45.5% of the patients with CLVH present and in 63.6% with CLVH absent, with no statistical difference (table 5).

Discussion

To date, BSS has been described in fewer than 300 patients. The current literature suggests that only 1 in 4 cases is reported, which enables an estimate of the disease at around 1 case per 10 million inhabitants[3]. The state of Rio Grande do Norte (Brazil) has a population estimated at 3 million inhabitants. Therefore, our group represents a significant sample, being sample size the largest in the world.

The occurrence of cardiovascular and metabolic abnormalities in patients with BSS is currently little discussed. In this study, the prevalence of paternal consanguinity; type II diabetes mellitus; insulin resistance; *acanthosis nigricans*; hepatomegaly; splenomegaly; decreased HDL-c; and increased TG was similar to those found in the literature (table1)[3, 6,10,11,14,15,17].

A relevant finding of this study was that MS was identified for the first time in patients with BSS. It was found in most of the patients: 18 (81.8%), 11 (78.6%) of whom were female. Of the 7 (31.81%) children and adolescents in this study, 6 had criteria for MS, 5 (71.42%) of whom were female and 1 (14.28%) male. The most prevalent criteria were low HDL-c (81.81%); hyperglycemia (77.27%); hypertriglyceridemia (63.63%); and SAH (50%). With respect to WC none of the patients showed an increase in this variable. The male patients had higher WC than the females, which results in higher preventive care in regard to cardiopathies (table 1). These findings were quite significant owing to the high incidence found in BSS and because they are representative of the increase in general mortality and in cardiovascular complications[24].

All patients showed poor control over fasting glucose, in addition to decreased HDL-c and increased TG. These results were similar to those found in the literature (table 1)[3,6,10,11,14,15,17]. The association between low HDL-c and elevated TG greatly increase the risk factors for cardiovascular diseases[24].

SAH was observed in 50% of the patients. These findings are in complete agreement with other authors who found it in 46.5% of the 13 case reports studied[2,8,16]. Prehypertension, not previously described, was identified in 27.3% of the patients. (table 1). This classification of prehypertension is particularly important for treating patients with MS and diabetes mellitus[24,26].

Another relevant finding from this study is related to the results obtained with the electrocardiogram and the chest X-ray. Neither

Table 2 – Echodopplercardiographic variables in 22 patients with Berardinelli-Seip syndrome by gender and their corresponding descriptive values.

Variable	Total (n = 22)	Males (n = 8)	Females (n = 14)	*p*- value
	n ± SD	n ± SD	n ± SD	
LA (cm)	3.21 ± 0.67	3.25 ± 0.72	3.18 ± 0.66	0.89
AO root (cm)	2.78 ± 0.30	2.92 ± 0.40	2.70 ± 0.21	0.20
IVSd (cm)	1.10 ± 0.28	1.09 ± 0.31	1.10 ± 0.27	0.91
LVIDd (cm)	4.24 ± 0.59	4.45 ± 0.58	4.12 ± 0.58	0.33
LVPWd (cm)	1.02 ± 0.29	1.03 ± 0.29	1.01 ± 0.29	0.89
LVIDs (cm)	2.28 ± 0.47	2.25 ± 0.38	2.30 ± 0.53	0.73
EF - Simpson (%)	67.3 ± 8.1	68.0 ± 4.7	66.9 ± 9.7	0.91
LV mass (gr)	158.1 ± 61.8	167.8 ± 56.4	152.5 ± 66.1	0.68
LV mass index (g/m^2)	99.0 ± 36.4	94.1 ± 32.0	101.8 ± 39.6	0.56
LVI – Peak E (m/s)	0.90 ± 0.14	0.87 ± 0.18	0.92 ± 0.11	0.18
LVI – Peak A (m/s)	0.66 ± 0.12	0.59 ± 0.12	0.69 ± 0.11	0.060
E/A ratio	1.39 ± 0.20	1.48 ± 0.25	1.33 ± 0.14	0.18
LVI – Peak E during VM (m/s)	0.77 ± 0.15	0.71 ± 0.18	0.81 ± 0.13	0.12
LVI – Peak A during VM (m/s)	0.61 ± 0.13	0.57 ± 0.12	0.63 ± 0.13	0.24
E/A ratio during VM	1.29 ± 0.23	1.28 ± 0.32	1.30 ± 0.18	0.89
LV isovolumic relaxation (m/s)	80.0 ± 10.69	73.75 ± 9.16	83.57 ± 10.08	0.03
Mitral E-wave deceleration time (m/s)	160.0 ± 15.43	158.75 ± 18.08	160.71 ± 14.39	0.83
Variable	**n (%)**	**n (%)**	**n (%)**	***p- value***
Normal echodopplercardiogram	9 (40.9)	4 (50)	5 (35.7)	0.41
Mild mitral regurgitation	6 (27.3)	1 (12.5)	5 (35.7)	0.25
Calcific aortic valve	2 (9.1)	0 (0)	2 (14.3)	*
Mild aortic regurgitation	1 (4.5)	0 (0)	1 (7.1)	*
LV systolic dysfunction	1 (4.5)	0 (0)	1 (7.1)	*
Concentric LV hypertrophy	11 (50)	4 (50)	7 (50)	*
Eccentric LV hypertrophy	1 (4.5)	0 (0)	1 (7.1)	*
Normal LV geometry	10 (45.5)	4 (50)	6 (42.9)	0.54

*Values expressed as mean ± standard deviation (SD); LA - left atrium; AO - aorta; IVSd - inter-ventricular septum end-diastolic thickness; LVIDd - left ventricular end-diastolic diameter; LVPWd - left ventricular posterior wall end-diastolic thickness; FE - ejection fraction; LV - left ventricular; LVI - left ventricular inflow; E - peak velocity of early diastolic filling of mitral inflow; A - late diastolic filling due to atrial contraction; VM - Valsalva maneuver; IVRT -left ventricular isovolumic relaxation time. *Few cases: <5 patients present or absent*

of these parameters was useful in identifying the presence of cardiac abnormalities in BSS, particularly the presence of LVH. Unlike other studies, which often found cardiomegaly in chest-X-rays[7,8,11,13,16], only 1 case was observed in the present work (datum not shown). Therefore, to identify cardiovascular damage, an echodopplercardiographic study was indispensable.

With respect to the echocardiographic abnormalities in this study, a high prevalence of cardiac damage was found, through

Table 3 – Relationship between frequency (n) and percentage (%) of left ventricular hypertrophy on electrocardiogram and clinical parameters with echodopplercardiogram (normal or abnormal) in 22 patients with Berardinelli-Seip syndrome.

Variable	Normal echodoppler		Abnormal echodoppler		*p*-value
	n = 9		n = 13		
	n	%	n	%	
LVH (ECG)	0	0	4	30.8	*
Diabetes mellitus	5	55.6	10	76.9	0.27
Hepatomegaly	7	77.8	13	100	*
Splenomegaly	2	22.2	8	61.5	0.082
SAH + Prehypertension	5	55.6	12	92.3	*

*Echodoppler - echodopplercardiogram; LVH - left ventricular hypertrophy; ECG - basal electrocardiogram; SAH - systemic arterial hypertension; *Few cases: <5 patients present or absent*

Table 4 – Frequency (n) and percentage (%) of left ventricular hypertrophy on electrocardiogram and clinical parameters with respect to concentric left ventricular hypertrophy on echocardiogram (presence or absence) in 22 patients with Berardinelli-Seip syndrome.

Variable	CLVH present		CLVH absent		*p*-value
	n=11		n=11		
	n	%	n	%	
LVH (ECG)	4	36.4	0	0	*
Diabetes mellitus	8	72.7	7	63.6	0.50
Hepatomegaly	11	100	9	81.8	*
Splenomegaly	7	63.6	3	27.3	0.099
SAH + Prehipertensão	10	90.9	7	63.6	*

*CLVH: concentric left ventricular hypertrophy; LVH : left ventricular hypertrophy; ECG: basal electrocardiogram; SAH: systemic arterial hypertension; *Few cases: <5 patients present or absent*

Table 5 - Relationship between arrhythmia on the Holter and chronotropic incompetence on the ergometric test with concentric left ventricular hypertrophy on echocardiogram in 22 patients with Berardinelli-Seip syndrome.

Variable	CLVH presente		CLVH absent		*p*-value
	n = 11		n = 11		
	n	%	n	%	
Holter: normal	2	18.2	4	36.4	0.25
Holter: ventricular ectopic beats	6	54.6	6	54.6	0.54
Holter: supraventricular ectopic beats	9	81.8	6	54.6	0.16
Holter: sustained supraventricular tachycardia	3	27.3	1	9.1	*
Holter: first-degree atrioventricular block	0	0	1	9.1	*
ET: chronotropic incompetence	5	45.5	7	63.6	0.54

*CLVH: concentric left ventricular hypertrophy; Holter: 24-hour ambulatory electrocardiogram monitoring; ET: exercise testing; * Few cases: <5 patients present or absent*

the presence of CLVH (50%) in both genders, a finding similar to that of other authors[7,8,14,15,17]. On the other hand, no case of hypertrophic cardiomyopathy was detected, although it has been widely reported in the literature as a frequent finding[6-8,11-13,15,38]. Eccentric left ventricular hypertrophy was observed in 4.5% of the patients. Mild mitral regurgitation was found in 6 patients with BSS. Only 1 patient showed global left ventricular hypokinesis and systolic dysfunction (table 2).

Insulin resistance and cardiopathies

The possibility of insulin resistance causing myocyte hypertrophy is the likely histopathologic link, given the increased fiber diameters and absence of criteria for hypertrophic cardiomiopaty. Indeed, this cardiomyopathy occurs in patients with insulin resistance syndrome through the direct action of insulin on insulin-like growth factor (IGF-1) receptors[10]. The high frequency of this pathology, associated to concentric hypertrophy in these patients was also reported by Klar et al[12] in 1993. In autopsy findings, the fibers were arranged without glycogen deposits and fat infiltration[8,13]. Hypertrophic cardiomyopathy associated to diabetes melitus is often linked to ventricular dilation and coronary artery alterations[13]. In the present study, only 1 patient was found with increased inner LV diameters (eccentric hypertrophy) (table 2). The histologic differentiation with classical hypertrophic cardiomiopaty is due to the absence of fiber disarrangement in lipodystrophy-associated hypertrophy[12,14].

Unlike other studies that identified high rates of diastolic dysfunction through the assessment of transmitral flow[7,8,13,14], no left ventricular diastolic dysfunction was found in any of our patients, even after the Valsalva maneuver was used. Another finding that differed from the literature[8,11,15,38,39] was the presence of systolic dysfunction. Only 1 patient in this study had left ventricular systolic dysfunction. One of the limitations of this work was the non-use of tissue Doppler imaging, which is as yet unavailable at our facility.

Holter recordings identified high rates of cardiac arrhythmia in patients with BSS. Despite the low mean age (22.4% ± 9.7 years) of these patients, 54.6% exhibited ventricular ectopic beats with CLVH present, and another 54.6% with CLVH absent (table 5). There is only one report in the literature: a 5-year-old patient, who was monitored for 24 hours, showing normal Holter[38].

With respect to exercise testing, chronotropic incompetence was observed in 45.5% of the patients with CLVH present and in 63.6% of patients with CLVH absent (table 5). Exercise testing was normal for myocardial ischemia in the patients who attained the desired heart rate and in those who displayed chronotropic incompetence. There was no relationship between chronotropic incompetence and CLVH present or absent. The presence of chronotropic incompetence is a predictor of increased cardiac mortality and incipient coronary disease, given that the desired heart rate is not achieved[40]. The significant relevance of this finding lies in the fact that there are no reports in the literature correlating exercise testing and chronotropic incompetence in patients with this syndrome.

Finally, sudden death is reported in the few cases with cardiac alterations. The relationship between cardiac alterations and dyslipidemia is described as a cause of sudden death in BSS[8,12]. Cardiac alterations increase with age[7,8], a finding not corroborated in the present study.

Conclusion

The results obtained reveal cardiovascular and metabolic abnormalities, with a high prevalence in young, asymptomatic patients with BSS. These findings point to the need for cardiological follow-up and preventive measures in this high-risk group.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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