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Clinical Course of Patients with Bartter Syndrome

Jose Henrique Paiva Rodrigues,[1] Luiz Alberto Wanderley Menezes Silva,[1] Silvia Bouissou Morais Soares,[2] Raissa Ritielle Olivia Cruz,[2] Flavia Cristina de Carvalho Mrad,[1,2] Ana Cristina Simoes e Silva[1,2]

[1]Interdisciplinary Laboratory of Medical Investigation, Faculty of Medicine, Federal University of Minas Gerais (UFMG), Brazil
[2]Pediatric Nephrology Unit, Faculty of Medicine, UFMG, Brazil

Original Paper

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Introduction. Bartter syndrome (BS) is a salt losing tubulopathy due to impairment of the transport mechanisms at the thick ascending limb of the Henle's loop. The aim of this study was to report the clinical course of patients with BS.

Methods. Patients with BS were followed from 1996 to 2020 and enrolled to a systematic protocol to confirm primary BS by evaluating the metabolic derangements, nephrolithiasis and nephrocalcinosis. Treatment was based on standard guidelines. Comparisons were made between data at baseline and at the last visit.

Results. A total of 13 patients (7 males) with primary BS were analyzed. Two patients had a mutation of the KCNJ1 gene. Age at diagnosis was 3 ± 4.5 years and the follow-up period was 11.19 ± 6.76 years. Metabolic alkalosis was initially detected in 76.92% and remained stable at the last visit ($P > .05$). Hypokalemia was present in 61.5% of patients at diagnosis, but sustained in 38.46% at the last visit ($P < .05$). Urine calcium level was 13.3 ± 9.6 mg/kg/d at the first visit, and significantly reduced to 3.7 ± 2.0 mg/kg/d at the last visit ($P < .05$). Nephrocalcinosis was detected by first kidney ultrasonography in 53.8% of patients. Kidney function was preserved, with a glomerular filtration rate of 120.1 ± 28.7 mL/min/ 1.73m^2 at last visit. Growth was completely recovered in 71.42% and partially improved in 14.28% of patients after treatment, respectively. All patients received indomethacin and potassium chloride salts.

Conclusions. Long-term follow-up of this cohort of BS showed favorable outcomes after treatment resulting in metabolic normalization and growth catch-up in most patients.

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INTRODUCTION

Bartter syndrome (BS) is an inherited renal tubular disorder caused by defective salt reabsorption in the thick ascending limb of Henle's loop.[1] BS presents as five different subtypes based on molecular genetics, while cases of acquired forms have also been reported.[1-4]

All forms of BS present with chronic renal loss of sodium, chloride and potassium, and inability to regulate urinary concentration with consequent polyuria, hypovolemia, hypokalemia, hyponatremia, hypochloremia, metabolic alkalosis, hypercalciuria and progressive medullary nephrocalcinosis.[1-3] As a compensatory mechanism, renin production is increased, leading to activation of the renin-angiotensin system with increased local production of Angiotensin II (Ang II), resulting in high concentrations of prostaglandin E2 (PGE2)

and stimulation of aldosterone release. Ang II stimulates the vasoconstriction of glomerular efferent arteriole, whereas PGE2 causes vasodilation of the afferent arteriole. Both changes result in glomerular hyperfiltration.[2,3,5,6] If BS is diagnosed early and treated promptly, the prognosis would improve. [2,3,7-9]

In this context, the present study aimed to report the clinical course of a cohort of 13 patients with BS followed from 1996 to 2020, emphasizing on the improvement of clinical and laboratory parameters with treatment and the occurrence of side effects and complications.

MATERIALS AND METHODS

In this retrospective cohort study, data from 13 patients with primary BS, who were consecutively admitted to our Pediatric Nephrology Unit from March 1996 to March 2020 were analyzed. Patients with a confirmed diagnosis of BS based on clinical, laboratory and imaging findings were included and patients whose diagnostic workups were not sufficient to confirm the diagnosis of BS, and those whose medical records had insufficient data for analysis were excluded.

To exclude other causes of metabolic alkalosis, we measured urine electrolytes, sought the characteristics of the activation of the renin-angiotensin system and verified the absence of use of diuretics and antacids by the patients.

Totally, 13 patients with a confirmed diagnosis of BS based on clinical, biochemical and ultrasonographic findings were included and followed for 24 years from 1996 to 2020.

For all patients we followed a systematic protocol at our institution, including detailed clinical history, physical examination, serial laboratory tests, including measurements of blood gas and concomitant urinary PH, serum levels of creatinine, urea, electrolytes and 24-hour urine collection for electrolyte and creatinine. Kidney and urinary tract ultrasound were repeated at least annually. Visits were scheduled periodically for about two to six months.

The evaluated variables were gender, age at diagnosis, clinical presentation, follow-up duration, and laboratory and imaging data. The analyzed data were obtained at the time of diagnosis and the last medical visit.

Anthropometric data were collected in all visits. Weight and height data were normalized based on data from the World Health Organization for children[11] or the 2000 Center for Disease Control data for adults.[12]

Adequate metabolic control was defined as plasma or serum bicarbonate between 22.0 to 26.0 mmol/L. Hypercalciuria was defined as 24-hour urinary calcium excretion higher than 4 mg/kg/day or spot-urine calcium/creatinine ratio above the upper limit of normality according to age range.[13,14] Glomerular filtration rate (GFR) was estimated by the updated Schwartz formula.[15,16] An ultrasound scan evaluated the presence of nephrocalcinosis, which was defined as a diffuse calcification of the renal pyramids.[17]

Treatment was based on standard guidelines, which generally included lifelong fluid and electrolyte supplementation and control of hypercalciuria. Nonsteroidal anti-inflammatory drugs (NSAIDs) were also used to inhibit excessive PGE2 synthesis. Cyclooxygenase-2 (COX-2) inhibition, mainly with Indomethacin, prevents the occurrence of high levels of PGE2 in BS patients. The recommended dose of Indomethacin ranged 1 to 3 mg/kg/d in two or three divided doses.[1,2,18]

Statistical Analysis

Statistical analysis was performed using SPSS Statistics Version 22.0 (IBM Corp, Armonk, NY). Continuous variables were presented as mean and standard deviation (SD) for and categorical variables as proportions. Weight-for-age (WAZ) and height-for-age (HAZ) Z-scores were used to assess weight and stature, respectively. These parameters were calculated with the public domain software EPI-INFO (version 7.0). The normality of the distribution was evaluated by the Kolmogornov–Smirnov test. The delta HAZ or delta WAZ was calculated as HAZ or WAZ at last visit minus HAZ or WAZ at baseline, respectively. The delta bicarbonate (BIC) was calculated as bicarbonate level at last visit minus bicarbonate level at baseline. The Mann-Whitney U Test and Kruskal-Wallis nonparametric test were used to compare medians of delta HAZ or delta WAZ. The chi-square test was used to compare categorical variables at admission and the last visit. Paired t-test was used to analyze the changes in normally distributed continuous variables between baseline and last follow-up. To further analyze the association between baseline

factors and growth improvement, the response variable was set as an increase of at least one SD in WAZ or HAZ at the last visit. The following variable were assessed as independent predictors: baseline levels of bicarbonate, potassium, chloride, creatinine, phosphate; nephrocalcinosis (present or absent) and calcium to weight ratio at baseline; sex; etiology (primary or non-primary); variation in bicarbonate levels during follow-up (delta BIC); age at diagnosis as continuous and as a categorical variable (age 2: ≤ 36 months and > 36 months; based on the median value and age 3: ≤ 96 months and > 96 months, based on the third quartile value); age of the patient at baseline as continuous and as a categorical variable (age 2: ≤ 37 months and > 37 months, based on the median value and age 3: ≤ 90.5 months and > 90.5 months, based on the third quartile value) and follow-up duration as continuous and as a categorical variable (follow-up ≤ 141 months and > 141 months, based on the median value).

The analysis was conducted in two steps. In the first step, univariate analysis was performed by Chi-Square Test with Yates correction for comparison of proportions between growth parameters and clinical features and Kruskal Wallis Test to compare growth parameters with continuous variables at admission. Then, a logistic regression model was applied to identify variables that were independently associated with the gain of one standard deviation (SD) in HAZ and WAZ. Only those variables that were found to present different proportions in univariate analysis ($P < .05$) were included in the regression model. Variables that retained a significant independent association ($P < .05$) were included in the final models.

The Ethics Committee of the Federal University of Minas Gerais approved the study under the protocol number 144/02.

RESULTS

Demographic Data

A total of 13 patients (7 males, 53.8%) with BS were analyzed with no patient exclusion. The median age at diagnosis and age at baseline were 3.0 years (3 months to 15 years) and 4.6 years (4 months to 15 years), respectively. The median follow-up time was 11.7 years (3 months to 22 years). Eleven (84.6%) patients had been followed for more than five years. Data regarding gender differences can be found in Table 1. The primary type of the disease was the only form of BS present in this cohort and the disease was confirmed in two patients (15.4%), who were sisters, by using genetic testing (KCNJ gene mutation).[19] In this cohort, we identified a total of three patients born to consanguineous parents (first cousins). However only the two mentioned sisters were identified as siblings. There were statistical differences in age at diagnosis ($P < .05$) and age at baseline ($P < .05$), between the genders. Mean values of these parameters are described in Table 1. Age at diagnosis as a categorical parameter was also associated with gender. All 7 male participants were diagnosed at age less than 8 years and only 2 (33%) of the 6 female patients had the diagnosis made below this age ($P < .05$). The association between gender and age at baseline as a categorical parameter (age bellow 3 years-old and equal or above 3 years-old) was also observed. Six (85.7%) among 7 male patients were younger than 3 years, while only 1 (16.6%) of the 6 female patients was younger than 3 years of age ($P < .05$).

Clinical and Laboratory Findings at Baseline

At the beginning of the study, the most common findings were low weight, with 10 (76.9%) patients under -2 WAZ and seven (53.8%) patients under -2 HAZ. Polyuria and polydipsia were reported in eight patients (61.5%). Ultrasonography had been performed at baseline, detected nephrocalcinosis in seven (53.8%) patients. Three (23.1%) patients had a history of polyhydramnios. Other signs and symptoms are listed in Table 1. No patient had sensorineural deafness in our cohort.

Main laboratory findings at diagnosis included glomerular hyperfiltration in 11 (84.6%), hypochloremia in eight (61.5%), hypokalemia in eight (61.5%), hypercalciuria in eight (61.5%) and metabolic alkalosis in seven (53.8%) patients. Six (46.1%) patients had alkaline urine at baseline, five (38.5%) had hyposthenuria, four (30.7%) had hyponatremia, and three had (23.1%) patients revealed mild hyperkalemia. Five (38.5%) patients presented simultaneously with low weight and low height for age, hypokalemia, polyuria, and polydipsia. Mean GFR (Glomerular filtration rate) at the baseline was 140.76 ± 74.07 mL/min/1.73m^2. Comparison between laboratory findings at baseline and at last visit is shown in Table 2.

Table 1. Clinical Characteristics and Laboratory Findings at Baseline

Features	Female	Male	Total	*P*
	6	7	13	
Age at Diagnosis, y*	8.00 ± 5.01	0.91 ± 1.83	3.00 ± 4.55	.05
Age at baseline, y*	7.54 ± 4.20	1.58 ± 1.35	4.60 ± 4.44	.05
Etiology				
Primary	6	7	13	
Family history (n)				
Present	2	2	4	
Absent	4	5	9	
Presentation (n)				
Low Weight Gain	4	6	10	
Polyuria	6	2	8	
Polydipsia	6	2	8	
Growth Failure	3	4	7	
Polyhydramnios	2	1	3	
Development Delay	1	2	3	
Prematurity	2	0	2	
Dehydration	1	1	2	
Vomit	0	2	2	
Malnutrition	0	1	1	
Diarrhea	0	1	1	
Constipation	1	0	1	
Weakness	0	1	1	
Consanguineous Parents	3	0	3	
Image evaluation findings (n)				
Nephrocalcinosis	4	3	7	
Follow-up duration, y*	9.87 ± 4.40	17.5 ± 8.79	11.7 ± 7.26	

*Data are given as mean ± SD, with the standard deviation given in parenthesis

Table 2. Comparison Between Laboratory Findings at Baseline and at Last Visit in BS Patients

	At Baseline			At Last Visit			
	Female	Male	Total	Female	Male	Total	*P*
Bicarbonate, mmol/L*	26.93 (4.56)	31.70 (5.22)	29.5 (5.33)	27.45 (1.70)	34.95 (3.5)	31.49 (4.8)	> .05
Serum PH*	7.43 (0.09)	7.49 (0.09)	7.46 (0.09)	7.38 (0.02)	7.41 (0.06)	7.40 (0.05)	< .05
Base Excess*	4.05 (4.32)	6.87 (5.01)	5.56 (4.74)	1.71 (2.12)	8.15 (4.31)	5.18 (4.72)	> .05
PCO_2*	44.83 (7.73)	40.10 (7.72)	42.68 (7.73)	42.66 (7.71)	53.48 (5.83)	47.58 (8.67)	> .05
Sodium,* mmol/L	136.16 (2.31)	134.71 (3.72)	135.38 (3.12)	138.16 (2.13)	140.14 (4.05)	139.23 (3,34)	< .05
Potassium,* mmol/L	3.05 (0.98)	2.81 (0.92)	2.92 (0.92)	3.48 (0.57)	3.41 (0.56)	3.44 (0.54)	> .05
Chloride,* mmol/L	95.16 (9.33)	85.42 (7.80)	90.15 (9.74)	100.66 (5.98)	95.14 (4.6)	97.69 (6.07)	< .05
Calcium,* mg/dL	9.65 (0.57)	8.52 (3.7)	9.08 (2.59)	5.82 (4.02)	9.11 (2.02)	7.47 (3.49)	> .05
Phosphate,* mg/dL	5.43 (0.45)	5.05 (0.99)	5.23 (0.78)	3.91 (0.85)	4.32 (1.03)	4.13 (0.93)	< .05
Magnesium,* mg/dL	2.18 (0.19)	2.22 (0.24)	2.2 (0.3)	2.16 (0.3)	1.95 (0.26)	2.05 (0.29)	> .05
Creatinine,* mg/dL	0.37 (0.16)	0.37 (0.17)	0.37 (0.16)	0.59 (0.15)	0.65 (0.29)	0.62 (0.23)	< .05
Urea,* mg/dL	22.88 (14.33)	27.14 (18.51)	25.17 (16.18)	21.66 (8.40)	26.71 (8.76)	24.38 (8.64)	> .05
Urinary PH*	7.53 (0.84)	7.2 (0.83)	7.38 (0.81)	6.83 (0.68)	6.6 (0.41)	6.72 (0.56)	< .001
Glomerular Filtration Rate, **mL/min*	159.83 (62.13)	124.42 (84,15)	140.76 (74.07)	116 (38.02)	123.71 (20.45)	120.15 (28.76)	> .05
24h Urinary Calcium, mg/kg/d*	9.9 (1.0)	15.34 (2.49)	13.3 (9.65)	5.73 (1.9)	2.49 (0.81)	3.71 (2.05)	< .05

*Data are given as mean, with the standard deviation given in parenthesis.
**Glomerular filtration rate estimated by Swartz formula

Clinical and Laboratory Findings at the Last Follow-up Visit

Baseline Symptoms were no longer reported at last visit. Nephrocalcinosis was successfully prevented in all patients, except in seven patients who were diagnosed with this condition at baseline.

Most patients had preserved kidney function, with an estimated GFR of 120.15 ± 28.76 mL/ min/ 1.73m^2 at the last follow-up. Two (15.38%) patients were diagnosed with chronic kidney disease (CKD) at baseline, in one of whom GFR completely recovered and the other remained at CKD stage 2. Treatment consisted of indomethacin and supplementation of potassium chloride for all 13 patients. The mean dose of Indomethacin ranged from 1.11 ± 0.3 mg/kg/d at baseline to 1.01 ± 0.43 mg/kg/d at the last visit. The mean dose of potassium chloride ranged from 3.06 ± 2.22 mEq/ kg/d to 2.23 ± 1.73 mEq/kg/d. Ten (76.9%) patients also used sodium chloride during the study time (the mean dose at last visit was 4.05 ± 2.49 g/d). Hydrochlorothiazide was prescribed for 2 patients (15.3%) with hypercalciuria and nephrocalcinosis and spironolactone was used in 1 patient (7.7%).

At the last visit, there was an improvement in most electrolyte and metabolic disorders. Two (15.3%) patients remained with metabolic alkalosis at the end of the follow-up. Among the eight patients with basal hypokalemia (61.53%), five (62.5%) achieved complete normalization, two (25%) improved, one (12.5%) worsened, and another two developed this condition during the period of the study.

Seven of the eight patients with hypochloremia at baseline (87.5%) improved, while four (50%) recovered completely. Another five patients developed hypochloremia during the follow-up period. Of the 11 patients who presented with glomerular hyperfiltration, there was complete normalization in eight (72.72%) but one (9.09%) patient worsened. One patient remained with alkaline urine and hyposthenuria at last visit. Among the eight patients with hypercalciuria on admission, six (75%) completely normalized and two showed improvements. Hypercalciuria was successfully prevented in the remaining seven patients. A significant difference was observed in genders regarding baseline levels of chloride ($P < .05$), final bicarbonate ($P < .05$) and final base excess ($P < .05$), with male gender presenting worse mean levels in all these parameters (Table 2). Significant reduction in 24-hour urinary calcium excretion was also observed (13.3 ± 9.65 mg/kg/d at baseline vs 3.71 ± 2.05 mg/ kg/d at last visit, $P < .05$) (Figure 1).

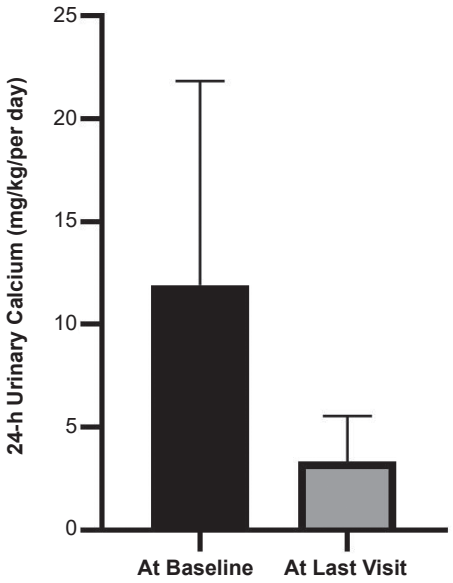

Figure 1. Comparison between 24-hour urinary calcium excretion (mg/kg/d) at baseline and at last visit in BS patients (*$P < .05$ (paired Student T test))

Growth Parameters Analysis

The mean HAZ at baseline was -2.6 (-4.59 to -0.62, SD = 1.50) and it reached -1.39 (-4.76 to +0.32, SD = 1.50) at the end of the study ($P < .05$, Figure 2). The mean female HAZ at baseline was -2.85 (-4.59 to -0.62, SD = 1.73) and it reached -1.84 (-3.92 to -0.46, SD = 1.15) at the last visit ($P > .05$). The mean male HAZ at baseline was -2.38 (-4.09 to -0.91, SD = 1.37) and it reached -1,00 (-4.76 to +0.32, SD = 1.73) at the end of the study ($P > .05$).

Differences and comparisons between genders are shown in Figure 2. According to the HAZ, among seven patients with growth impairment at the beginning of the study, five (71.42%) recovered utterly, one (14.28%) had partial recovery, and one (14.28%) had worsened z-score values. One patient (7.69%) that had normal growth at the beginning of the study developed growth impairment during the follow-up. At the last visit, 10 patients (76.9%) had a Z score above -2.

The mean WAZ at baseline was -3.41 (-6.14 to +0.04, SD = 2.04) and reached -2.08 (-6.63 to -0.11, SD = 2.06) at the end of the follow-up period ($P < .05$, Figure 3). The mean female WAZ at

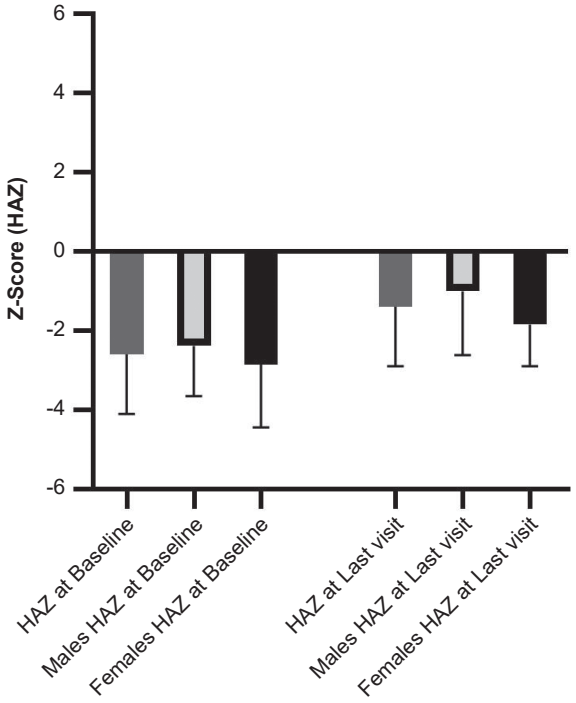

Figure 2. Height parameters of patients with Bartter syndrome at baseline and at last visit, (*P < .05) and height parameters of Bartter syndrome patients at baseline and at last visit according to gender

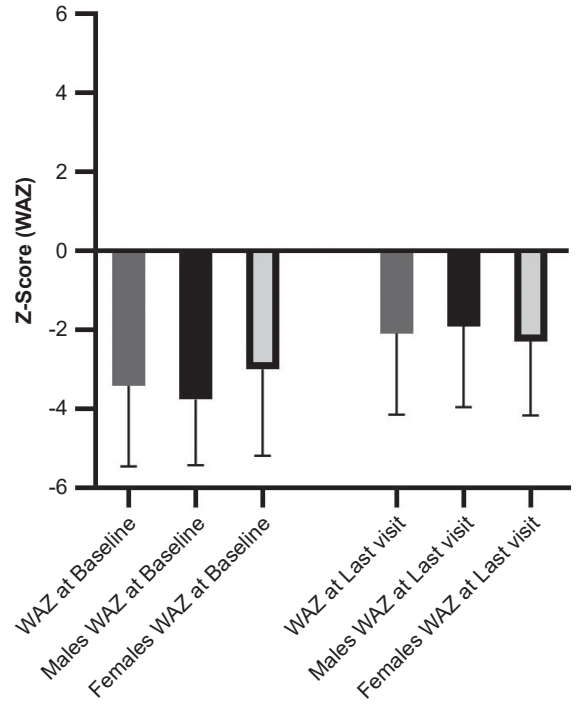

Figure 3. Weight parameters of patients with Bartter syndrome at baseline and at last visit. (P < .05) and weight parameters of patients with Bartter syndrome at baseline and at last visit according to gender

baseline was -2.995 (-6.06 to +0.04, SD = 2.39) and it reached 2.28 (-5.55 to -0.11, SD = 2.06) at the end of the follow-up period (P > .05) The mean male WAZ at baseline was -3.77 (range: -6.14 to -1.48, SD = 1.79) and it reached -0.95 (range: -6.63 to -0.3, SD = 2.2) at the end (P < .05, Figure 3). According to the WAZ, among 10 patients with low weight at baseline, five (50%) completely regained weight, three (30%) had partial recovery, and two (20%) worsened. At the end of the follow-up, 8 (61.5%) patients had a Z score above -2.

Follow-up duration (P > .05) and final potassium levels (P > .05) were included in the regression model. However, neither of these parameters were significantly associated with HAZ gain. For WAZ gain, sex (P > .05), follow-up duration (P > .05), potassium levels at baseline (P > .05) and at last visit (P > .05), phosphate levels at baseline (P > .05) and final creatinine levels (P > .05) were also included in the regression model.

DISCUSSION

The results of our study are derived from the follow-up of patients with BS at a reference center for an average duration of 11 years. Among our patients, 84.6% were followed for at least five years, showing adequate adhesion to treatment and clinical and growth improvement. Like other recent cohorts, the male gender (53.8%) slightly prevailed in our study.[8,18,20-22] However, it is impossible to determine whether BS is more prevalent in a specific gender due to the absence of extensive epidemiological data. All the parents were completely asymptomatic, supporting the autosomal recessive mode of inheritance.[3,23]

Primary BS was the only diagnosed form of the syndrome, and the mean age at diagnosis was 4.45 years. This is considered a late diagnosis in comparison to other cohorts, in which the mean ages at diagnosis were 17.5, 24.5 and 26 months.[7,9,24] Sampath Kumar *et al.* had an even younger patient, diagnosed at an average age of 6.5 months.[25] We believe that this late diagnosis of BS is due to late referral of the patients to our Pediatric Nephrology Unit. Pediatricians should be aware that BS is in the differential diagnosis of growth deficits and complaints of polyuria, polydipsia, vomiting and dehydration, with or without a history of polyhydramnios, that requires early referral.[2,3,7] We also found a statistically significant difference

between sex and age at diagnosis ($P < .05$), with female patients diagnosed at an older age compared to males in our study. There is no data in the literature which supports this finding, and the low number of patients in our study cannot let us to make a definite conclusion.

Failure to thrive, growth impairment, polyuria and polydipsia are the most common and frequently reported symptoms at baseline.[2,3,7,9,20,21,24-28] BS can cause polyhydramnios between the 20th and 30th weeks of pregnancy, leading to premature birth in most patients.[3,8,18,29] History of polyhydramnios was present in three of our patients (23.1%), two of whom were born prematurely. Another cohort of 19 patients with BS also reported 7 (36.8%) patients with this finding.[21] Two other larger cohorts of BS, including 34 and 35 patients, found a history of polyhydramnios in 75% and 65.7% cases, respectively.[8,22] The late diagnosis of BS and the absence of suspicion or confirmed diagnosis during pregnancy in our series may explain the difference in polyhydramnios data compared to other studies.

Nephrocalcinosis was detected in 53.8% of our patients, a finding similar to that reported by Han *et al.* 2019 (66%), but a higher percentage than other cohorts, including Kaur *et al.* (14%), Hee al. (20%) and Vaisbich *et al.* (25%), while another cohort of types I and II BS patients reported by Puricelli *et al.* showed a high prevalence of 93.3%.[8,9,18,24,29] The late diagnosis of BS in our patients, who also had severe hypercalciuria at baseline, may explain the common detection of nephrocalcinosis. At the beginning of the study, hypercalciuria was detected in eight (61.53%) of our patients, thatwas well controlled. None of our patients developed chronic kidney disease due to calcium deposition in the renal parenchyma.

In our study only two patients had reduced kidney function at diagnosis, but only one remained with CKD at the last visit. No other patient developed CKD during follow-up. Our results contrast with other studies that showed a higher prevalence of CKD, especially in patients with BS type I and BS type IV.[3,8,20] The cause of kidney dysfunction in BS remains unclear.[8] In addition to the molecular defect, other risk factors that potentially contribute to CKD may be prematurity, nephrocalcinosis, chronic dehydration, treatment with NSAIDs and proteinuria related to glomerular hyperfiltration.[2,3]

Growth impairment in BS results from several factors, including partial or complete GH deficiency, hypokalemia, and metabolic alkalosis.[2,3,7,8,30] In our study, correction of hypokalemia and metabolic alkalosis in most patients may, at least in part, explain the observed growth recovery. At baseline, we found 76.9% and 53.4% of our patients with Z score below -2.0 for height and weight for age curves, respectively. After treatment, there was a total growth recovery in five of them (71.42%). One patient (14.28%) had partial growth recovery, and only one had reduced the Z score values. Several other studies have also found impaired growth at the diagnosis and obtained adequate response and recovery after using indomethacin and/or electrolyte supplementation, similar to our study.[6,9,18,20,23,24] In our series, female patients had slightly lower HAZ at baseline. Male patients had better height recovery during follow-up with greater HAZ delta. We attribute these differences to the late diagnosis of our female patients.

The clinical and laboratory results of our case series at the end of the follow-up supports the general idea that if BS is detected early in life and properly treated, patients can have a good prognosis. Electrolytic supplementation, proper hydration, and control of hypercalciuria and glomerular hyperfiltration can result in normal growth, interrupting or even preventing nephrocalcinosis and CKD. Other cohorts also support this concept.[6,18,20,23,24]

This study has some limitations, especially the low number of patients from a single center. Besides, the biochemical data was evaluated at baseline and at the last visit, which may not represent the entire follow-up period. The number of kidney ultrasounds to monitor nephrocalcinosis in our patients may be another limiting factor in assessing this condition. Also, few genetic tests have been carried out due to their difficult availability. However, it should be emphasized that genetic testing in children with symptoms suggestive of BS makes the specific diagnosis and genetic counseling to family members possible.[3]

CONCLUSION

The long-term follow-up of this BS cohort showed a favorable evolution after treatment, resulting in metabolic normalization, preserved kidney function and growth recovery in most patients.

ABBREVIATIONS

BS: Bartter syndrome
Ang II: Angiotensin II
PGE2: Prostaglandin E2
GFR: Glomerular filtration rate
NSAIDs: Nonsteroidal anti-inflammatory drugs
COX-2: Cyclooxygenase-2
SD: Standard deviation
WAZ: Weight-for-age
HAZ: Height-for-age
BIC: Bicarbonate
CKD: Chronic Kidney Disease

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

FUNDING

No funding was demonstrated.

AUTHORS' CONTRIBUTIONS

FCCM, JHPR, LAWMS, SBMS and RROC collected patient's data, filled that data bank, and wrote the first draft. JHPR, LAWMS and SBMS performed statistical analysis. ACSS and FCCM conceptualized the study, made general supervision, and revised the manuscript. ACSS submitted the final version of the manuscript, which is approved by all authors.

DISCLOSURE STATEMENT

The authors have no competing interests.

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Correspondence to:
Ana Cristina Simoes e Silva, MD, PhD
Interdisciplinary Laboratory of Medical Investigation, Faculty of Medicine, UFMG, Av. Prof. Alfredo Balena, 190, Room # 281 - Belo Horizonte, MG, (Postal Code: 30130-100), Brazil Tel: 0055 31 3409 8073
E-mail: acssilva@hotmail.com

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