

Bartter's syndrome: evaluation of statural growth and metabolic profile

Síndrome de Bartter: avaliação do desenvolvimento estatural e perfil metabólico

Síndrome de Bartter: evaluación del desarrollo estatural y perfil metabólico

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ABSTRACT

Objective: Bartter's syndrome is one of the most important inherited diseases that cause chloride leak. The objective of this study was to report the follow-up of ten patients with the syndrome.

Methods: This observational study was based on the review of medical charts reporting the metabolic features, creatinine clearance, nutritional and anthropometric assessment of ten patients with Bartter's syndrome followed at the Nephrology Service of the Universidade Federal de São Paulo, in their first and last medical appointments, after a mean follow-up period of 43 months (3-76 months). During the follow-up, the management included the administration of potassium (100%) and magnesium (60%) supplements, non-steroidal anti-inflammatory agents (90%), angiotensin-converting enzyme inhibitors (40%) and spironolactone (50%). Statistical analysis was performed comparing the results of first *versus* last clinical appointment by non-parametric Wilcoxon test.

Results: Improvement of serum electrolytes and statural growth after the treatment was observed but only serum potassium {3.05mEq/L *versus* 3.25 mEq/L ($p=0.01$)} and weigh-for-age Z-score [initial median -2.47 *versus* -1.35 ($p=0.02$)] improved significantly. Out of the ten patients studied, two presented decrease of creatinine clearance with chronic kidney disease at stage 2 at the end of the follow-

up. These patients had already started the follow-up with decreased creatinine clearance.

Conclusions: There is a need of early treatment of patients with Bartter's syndrome in order to improve their electrolytes and nutritional condition without compromising the creatinine clearance.

Key-words: metabolic alkalosis; failure to thrive; polyuria; hypokalemia; developmental disabilities; Bartter syndrome.

RESUMO

Objetivo: A síndrome de Bartter é uma doença rara, porém uma das mais frequentes condições congênitas perdedoras de cloro. Este trabalho teve como objetivo relatar a evolução de dez pacientes com a síndrome.

Métodos: Estudo observacional, descritivo, realizado pela análise de prontuários médicos relatando o perfil metabólico, a depuração de creatinina, o estado nutricional e pôndero-estatural de dez pacientes atendidos no Serviço de Nefrologia da Universidade Federal de São Paulo com características clínico-laboratoriais da síndrome de Bartter, seguidos por um período médio de 43 meses (3-76 meses). Durante o acompanhamento, o tratamento consistiu na administração de suplemento de potássio (100%), magnésio (60%), anti-inflamatórios não hormonais (90%), inibidores

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de enzima conversora de angiotensina (40%) e espironolactona (50%). A análise estatística constou da comparação dos dados da primeira e da última consulta, utilizando-se o teste de Wilcoxon.

Resultados: Observou-se melhora dos valores absolutos dos itens avaliados e do desenvolvimento pâncreo-estatural com a terapêutica empregada, porém apenas a calcemia [mediana inicial 3,05mEq/L e final 3,25mEq/L ($p=0,01$)] e o escore Z de peso idade [mediana inicial -2,47 e final -1,35 ($p=0,02$)] apresentaram melhora significativa. Dos dez pacientes estudados, dois apresentavam diminuição da depuração de creatinina com doença renal crônica estágio 2 no final do acompanhamento (ambos tinham iniciado o acompanhamento com depuração renal comprometida).

Conclusões: Há necessidade da instituição terapêutica precoce para melhorar os níveis séricos dos eletrólitos e o estado nutricional dos pacientes acometidos, sem comprometer a depuração de creatinina.

Palavras-chave: alcalose metabólica; insuficiência de crescimento; poliúria; hipopotassemia; deficiências do desenvolvimento; síndrome de Bartter.

RESUMEN

Objetivo: El síndrome de Bartter (SB) es una enfermedad rara, pero una de las más frecuentes condiciones congénitas perdedoras de cloro. Este trabajo tiene por objetivo relatar la evolución de diez pacientes con SB.

Métodos: Estudio observacional, descriptivo, obtenido mediante análisis de prontuarios médicos. Relata el perfil metabólico, la depuración de creatinina, el estado nutricional y ponderoestatural de los diez pacientes atendidos en el ambulatorio de Tubulopatías de Universidade Federal de São Paulo con características clínico-laboratoriales de SB, seguidos por un periodo mediano de 43 meses (3-76 meses). Durante el seguimiento se practicó protocolo de tratamiento que consistió en la administración de suplemento de potasio (100%), magnesio (60%), anti-inflamatorios no hormonales (90%), inhibidores de enzima convertidora de angiotensina (40%) y espironolactona (50%). Se consideraron criterios de exclusión la presencia de alteraciones séricas y urinarias no compatibles con SB. El análisis estadístico constó de la comparación de datos de la primera y la última consulta, utilizándose la prueba de Wilcoxon.

Resultados: Se observó mejora numérica de los valores absolutos de los ítems evaluados y del desarrollo ponderoes-

tatural con la terapéutica utilizada, pero solamente la calcemia [mediana inicial 3,05mEq/L y final 3,25mEq/L ($p=0,01$)] y el escore Z de peso/edad [mediana inicial -2,47 y final 1,35 ($p=0,02$)] presentaron mejora significativa. De los 10 pacientes estudiados, dos presentaban reducción de la depuración de creatinina con enfermedad renal crónica etapa 2 y en el final del seguimiento (ambos habían iniciado el seguimiento con depuración renal comprometida).

Conclusiones: Los datos enfatizan la necesidad de la institución terapéutica precoz para mejorar los niveles séricos de los electrólitos y el estado nutricional, sin comprometer la depuración de creatinina.

Palabras clave: alcalosis metabólica; insuficiencia de crecimiento; poliuria; hipocalcemia; deficiencia del desarrollo; síndrome de Bartter.

Introduction

Bartter's syndrome (BS), which was first described in 1962, is characterized by hypokalemic, hypochloremic and hyperreninemic metabolic alkalosis, with normal blood pressure. Since its initial description, several forms of clinical presentation demonstrating the phenotypic heterogeneity of this disease have been observed^(1,2). In terms of clinical aspects, most patients are malnourished and have severe growth retardation (below the 3rd percentile)^(3,4). In addition, these patients present with polyuria, polydipsia, and dehydration, which occur in the neonatal period or early in life⁽⁵⁾. Studies of growth and development in patients with BS have suggested that severe growth retardation occurs during childhood and that normal height is rarely reached⁽⁶⁻⁸⁾. Bettinelli *et al* reported that the height of 18 children with BS ranged from -4.9 to 0.9 standard deviations, and 11 of these children had height below -2 standard deviations⁽⁸⁾.

Treatment includes non-hormonal anti-inflammatory agents and potassium replacement aiming to reduce or normalize the water-electrolyte balance of these patients, showing variable responses to therapeutic support, water and electrolyte replacement⁽⁹⁾. Schachter *et al* reported that the four patients they assessed had worsening of renal clearance after the association of non-hormonal anti-inflammatory drugs⁽⁹⁾.

The objective of the present study was to assess the impact of drug treatment on the metabolic profile and height and weight development of patients with BS treated between 2000 and 2006.

Method

During this observational and descriptive study, we analyzed the medical records of ten children with BS seen at the outpatient clinic of tubulopathy of the Unit of Pediatric Nephrology, Department of Pediatrics, Universidade Federal de São Paulo (Unifesp), between March 2000 and October 2006.

Considering the clinical and laboratory findings, BS diagnosis was established based on the criteria of hypokalemic and hypochloremic metabolic alkalosis, with increased prostaglandin and renin, and urinary losses of potassium, sodium, and chloride. All patients diagnosed with BS during the study period or who were being followed up at the outpatient clinic aged between three and 164 months (age at the beginning of treatment) were included in the present study. Exclusion criteria were presence of serum and urinary changes incompatible with BS.

These patients underwent serum tests in order to assess their levels of bicarbonate, potassium, pH, sodium, chloride, and magnesium, microalbuminuria in isolated urine sample and estimated creatinine clearance according to Schwartz formula⁽¹⁰⁾. As for creatinine, it was measured in blood and urine samples using the alkaline picrate method according to the modified Jaffé reaction⁽¹¹⁾. Serum creatinine was used to calculate estimated creatinine clearance according to Schwartz formula⁽¹⁰⁾. Urinary creatinine was used to calculate the relationship with the electrolytes. Venous serum bicarbonate was measured using a blood gas analyzer by means of the selective method (Ise) with the Advia 1650 Bayer device and normal values were set at 24-28mEq/L. Serum pH was measured using a blood gas analyzer by means of the selective method (Ise) with the Advia 1650 Bayer device, and normal values were set at 7.35-7.45. Electrolyte concentrations of serum sodium, potassium, and chloride were evaluated by the selective method (Ise), using the Advia 1650 Bayer device, and the normal value for sodium serum was 137-142mEq/L, while for potassium serum it was 3.5-5.2mEq/L and for chloride serum it was 98-107mEq/L. Serum magnesium level was measured using the colorimetric method (xylydyl blue), and the reference value was 1.8-2.2mEq/L. Microalbuminuria in an isolated urine sample was measured using immunoturbidimetry⁽¹²⁾.

Nutritional assessments were performed by nutritionists at the Unit of Pediatric Nephrology, using the direct method based on anthropometric measurements. Nutritional status was measured using body mass index (BMI), BMI z-score, weight for age and height for age z-scores for children based

on weight, height, sex and age of children and adolescents. These data were calculated using the software provided by the World Health Organization (WHO), Anthro and Anthro plus, which use the WHO curves as reference⁽¹³⁾. The WHO curves were used according to age group.

All patients underwent nutritional assessments during follow-up visits. The results of the assessment of the first visit were recorded and then the evolution was demonstrated based on the results of the last individual visit. It is important to emphasize that none of the visits included in the present study were emergency room visits, all of them being routine outpatient follow-up visits. Because BS is a rare pathology, we did not define minimal follow-up period as an exclusion criterion.

The treatment protocol included the use of non-hormonal anti-inflammatory drugs, especially indomethacin and potassium and/or magnesium replacement to keep the metabolic profile at normal or nearly normal levels in all patients. Other drugs, such as angiotensin I-converting enzyme inhibitor and spironolactone, were associated in some patients selected according to their clinical evaluation.

The statistical analysis consisted of comparison of each parameter at baseline and in the last follow-up visit, using means, medians, and minimum and maximum standard deviations to summarize and describe the patients. In order to compare quantitative variables at two different study times (beginning and end), we used the Wilcoxon test, with a limit of 5% ($p < 0.05$) to reject the null hypothesis. To demonstrate the temporal evolution of serum potassium serum levels, we designed a graph showing the values of each patient measured in semi-annual visits.

This study was approved by the Research Ethics Committee of Unifesp. The patients were not asked to sign a written consent form because this was a retrospective study and the Medical Ethics Committee of Unifesp did not require it.

Results

We evaluated ten children with BS who were followed up at our outpatient clinic during the study period. There were seven males and three females. The follow-up period ranged from three months to 76 months, with a mean of 44 months and median of 55 months.

The patients' age at the beginning of the follow-up ranged from three to 164 months, with a mean of 61 months. At the end of the study, the patients were eight to 230 months

old, with a mean age of 105 months. The onset of symptoms occurred in the neonatal period in one case, in the infant age group in seven patients, and in the preschool period in two children.

Of the ten patients, two had decreased creatinine clearance with chronic kidney disease stage 2 and 3 (patients 2 and 6) at the end of the follow-up period. These patients had already started the follow-up showing impaired renal clearance (stage 2).

In our sample, seven children used indomethacin during the follow-up period, two had previously used this drug and one did not use it. The medication dose ranged from

0.5 to 6.4mg/kg/day, and the mean dose was 2.2mg/kg/day. Among those who used indomethacin, two discontinued the medication because of gastrointestinal effects, but one patient resumed its use at low doses. Two patients who started being treated with indomethacin at other health care facility had upper gastrointestinal bleeding and epigastric pain and replaced indomethacin with diclofenac. These patients started being followed up at our outpatient clinic while using diclofenac. The medication dose ranged from 1.5 to 7.5mg/kg/day, and the mean dose was 4.4mg/kg/day.

Regarding the use of nimesulide, only one child received this drug because of side effects caused by indomethacin. The

Table 1 - Patients' laboratory and nutritional data

Laboratory and nutritional data	Baseline median (min/max)	Final median (min/max)	p
Creatinine Clearance (ml/min/1.73m ²)	82 (59/154)	101 (53/160)	0.959
Microalbuminuria (ug/min)	52 (1/311)	19 (0/288)	0.128
Serum pH	7.45 (7.25/7.71)	7.39 (7.30/7.55)	0.208
Serum bicarbonate (mEq/L)	28 (24/44)	26 (22/34)	0.440
Serum potassium (mEq/L)	3.0 (2.0/4.0)	3.2 (2.0/5.0)	0.010
Serum chloride (mEq/L)	92 (50/108)	99 (91/118)	0.079
Serum sodium (mEq/L)	136 (121/143)	138 (132/144)	0.139
Serum magnesium (mEq/L)	1.8 (1/3)	1.7 (2/3)	0.406
H/A z-score	-1.3 (-3.5/1.3)	-0.7 (-1.7/1.1)	0.114
W/A z-score	-2.5 (-3.8/-2.0)	-1.3 (-2.8/0.6)	0.028
BMI z-score	-2.1 (-4.2/2.0)	-1.3 (-2.8/0.8)	0.264

P: descriptive level of Wilcoxon's test; H/A z-score: height for age z-score; W/A z-score: weight for age z-score; BMI z-score: body mass index z-score; min: minimum, max: maximum.

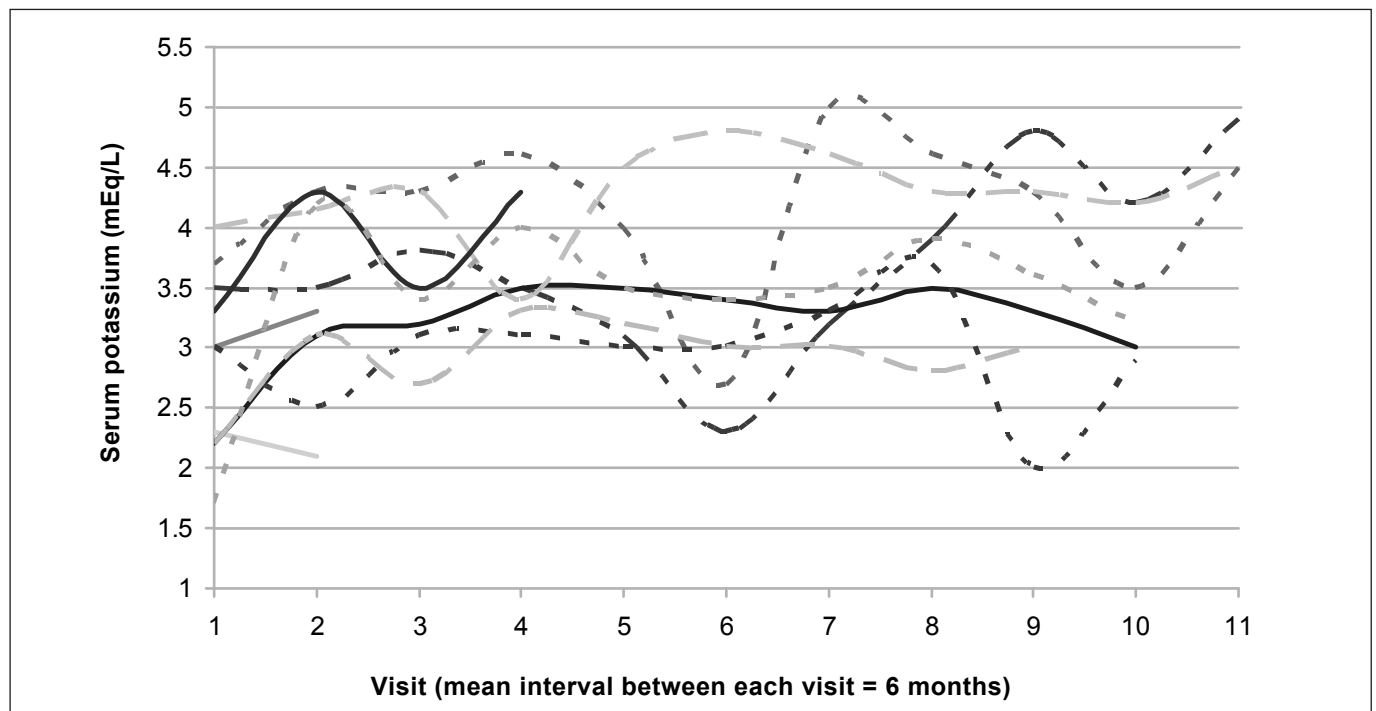


Chart 1 – Variation of the serum potassium levels of patients during follow-up (Each line represents one patient).

dose used was 5.2mg/kg/day. One patient replaced the anti-inflammatory used with rofecoxib to reduce gastrointestinal effects of the first drug. The medication dose for this patient ranged from 1.3 to 11.6mg/kg/day, and the mean dose was 9.1mg/kg/day.

Spironolactone was administered to five children at doses of 0.5 to 6mg/kg/day, and the mean dose was 2.4mg/kg/day. Angiotensin I-converting enzyme inhibitor was given to four patients at doses ranging from 0.3 to 4.9mg/kg/day and a mean dose of 1.21mg/kg/day.

All patients required some type of oral potassium replacement (0.1 to 44mEq/kg/day, mean of 5mEq/kg/day). Six patients required replacement of magnesium at some point of the follow-up period, with doses of 1.7 to 24.9mg/kg/day and a mean dose of 10.2mg/kg/day.

There was a trend of improvement of serum bicarbonate, pH, and electrolytes, without changes in the creatinine clearance; however, only the increase in the serum potassium level was statistically significant, even when using anti-inflammatory drugs as shown in Table 1. Chart 1 shows a trend to improved levels of serum potassium, evidencing an individual variation during follow-up. Furthermore, there was a statistically significant improvement between baseline and final values of weight for age z-score (Table 1).

Discussion

BS is one of the major causes of congenital chloride-losing diarrhea. This disorder has a heterogeneous spectrum, considering both clinical and laboratory factors. The early identification of this pathology is an important strategy for preventing morbidity and mortality, especially with regard to factors that are potentially preventable.

Five genetic variants of SB have been described. All these diseases are characterized by autosomal recessive transmission, except for type V, being caused by homozygous or heterozygous mutations directly or indirectly involving proteins responsible for the reabsorption of chloride in the thick ascending limb of loop of Henle⁽¹⁴⁾.

Since the first report on SB, clinical descriptions of patients have suggested that this disease is phenotypically heterogeneous. Throughout the years, two phenotypic groups have been described to encompass the gene mutations linked to BS: neonatal (NNBS) and classic (CBS). In the neonatal form, symptoms usually start before birth with the development of polyhydramnios between 23 and 30 weeks of

gestation. After birth, the following symptoms may develop: prematurity, polyuria, hypercalciuria, and nephrocalcinosis. One exception to this neonatal evolution is the NNBS type IV, which is associated with a mutation in the BSND gene. In this case, in addition to the findings of NNBS, patients also have deafness without nephrocalcinosis. On the other hand, the classic form affects infants and preschoolers with symptoms similar to but less severe than those present in the NNBS, growth deficiency, dehydration, and hypercalciuria without nephrocalcinosis⁽¹⁵⁾. In our sample, there was one case with onset of symptoms during the neonatal period, associated with hypoacusis and hypercalciuria without nephrocalcinosis; seven patients were infants and two were preschoolers. The neonatal case may be related to the mutation in the BSND gene; however, further molecular investigation should be conducted for more detailed information.

The development of chronic renal failure has been described in patients with BS, being caused by changes in the glomeruli and interstitium, secondary to the long period of hypokalemia and decreased renal perfusion, with repeated episodes of ischemic injury as a consequence of hypovolemia^(16,17). The two patients who showed worsening renal function at the end of the follow-up period started being followed up with some degree of renal function impairment, probably secondary to episodes of acute kidney injury and metabolic disorder before the diagnosis. In general, we did not find worsening of the creatinine clearance during the follow-up period in our sample.

BS belongs to a small group of tubulopathies characterized by a decrease in NaCl transport in renal distal nephron⁽¹⁸⁾. As a consequence, patients present with typical characteristics, including salt wasting, hypokalemic metabolic alkalosis, hyperreninemic hyperaldosteronism with normal blood pressure and alkaline urine pH. Studies on growth and development of patients with BS have suggested that there may be severe growth retardation in infants and preschoolers. According to Rudin, patients with BS may be underweight for their age and they rarely reach normal height^(15,17). Longitudinal growth retardation is a common symptom in diseases associated with hypokalemia in childhood. In the present study, despite the small number of patients, we found that the metabolic profile and weight and height deficit can be improved or recovered after the beginning of specific treatment. We found that in general there was difference between the baseline and final values for pH, bicarbonate,

and electrolytes, and between height for age, weight for age, and BMI z-scores, suggesting that the medications associated with multidisciplinary follow-up made it possible to improve growth.

The exact mechanism by which indomethacin improves linear growth has not been well defined, without any evidenced relationship with the medication dose; however, it is clear that despite growth retardation, height can be recovered with treatment⁽¹⁹⁾. In our study, patients who showed no improved height were followed up for a short period of time (patient four - 4 months) or low adherence to treatment (patient seven). Improvement can also be a consequence of an increase in serum potassium balance, since this ion is essential for longitudinal growth. The mechanism responsible for this has not been well established, but it may be associated with changes in the growth hormone secretion and resistance against its action⁽⁷⁾.

Because BS is a rare disease, there are few reports in the literature about nutritional data, which makes it difficult to establish comparisons with our results. Our study has a relatively long mean follow-up; however, we included patients who were only followed up for three months, which restricts the possibility of investigating the impact of the treatment on the disease progression in a broad manner. However, despite the limitation related to our small sample and the fact that we did not conduct any molecular investigations, the present study may contribute to make the clinical aspects and the treatment of this condition more widely known. After the beginning of the specific treatment, we found a trend of improvement in the metabolic profile and nutritional status, with resolution of the weight deficit in most patients. In conclusion, it is advisable to be aware of the possibility of establishing BS diagnosis so that therapeutic measures can be implemented as early as possible.

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