Residência Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 09/09/2020
Approved on: 14/10/2020

CASE REPORT

Bartter syndrome as a cause of growth delay and sensorineural hearing loss

Lorena Lago de Menezes[1], Luísa Lemos Pimentel[2], Lavinia Lago de Menezes[1], Diego Augusto Alves Rosa[1], Maylon Rudney de Sousa Ferreira[1]

Keywords:
Bartter Syndrome,
Alkalosis,
Hearing Loss,
Sensorineural,
Failure to Thrive.

Abstract

Bartter syndrome (BS) is a rare renal tubulopathy, which typically becomes apparent during childhood. It is caused by an autosomal recessive inheritance which involves the kidneys' ability to reabsorb sodium. This report depicts a case of an 18 month-old patient with several manifestations suggesting BS, such as hypokalemia, hypercalciuria, metabolic alkalosis, polyuria, polydipsia, growth delay and congenital bilateral sensorineural hearing loss. The diagnosis was confirmed after a genetic test by classifying the patient as type IV BS. In this context, knowing about BS is crucial to include it in the differential diagnosis of early onset tubulopathies. Therefore, the possible impacts of this condition can be minimized, leading to a better quality of life for the affected.

[1] University of Brasília, Medical School - Brasília - DF - Brazil.
[2] Brasília University Hospital, Department of Pediatrics - Brasília - DF - Brazil.

Correspondence to:
Lorena Lago de Menezes.
University of Brasília - UnB - Brasília, DF, Brazil. CEP 70297-400. E-mail: lorenalago.m@hotmail.com

Residência Pediátrica; 2023: Ahead of Print.
DOI: 10.25060/residpediatr-2023.v13n1-469

This work is licensed under a Creative Commons Attribution 4.0 International License.

INTRODUCTION

Bartter's Syndrome (BS) is a rare renal tubulopathy, with an annual incidence estimated by Rudin of 1.2 cases per million people, which usually appears during childhood, resulting from an autosomal recessive genetic inheritance[1]. The rarity is explained, in part, by the perinatal deaths that precede the probable diagnosis[2].

The mutations involved in BS cause impaired tubular reabsorption of sodium chloride (NaCl) in the thick ascending limb of the loop of Henle, explaining the metabolic alterations characteristic of BS: metabolic alkalosis, hypokalemia, hyperreninemia/hyperaldosteronism associated with normal blood pressure levels and high levels of E2 prostaglandin[3,4].

Clinically, the picture involves polyuria, polydipsia and delayed growth and development[5]. In some cases, hypercalciuria, hypomagnesemia and nephrocalcinosis are also present[2]. Additionally, specific mutations that compromise the CIC-Ka and CIC-Kb chloride channels are associated with the prenatal presentation of BS and bilateral sensorineural hearing loss, a unique complication of type IV BS[5,6].

Treatment is based on electrolyte supplementation (sodium chloride and potassium chloride) and fluid replacement, which may be associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) or potassium-sparing diuretics (PPD)[2]. The main NSAID used in pediatric patients is indomethacin, which must be monitored for its side effects on the gastrointestinal tract and kidneys. Spironolactone or amiloride, both DPP, may be useful in raising serum potassium levels and reversing metabolic alkalosis, however, they are contraindicated in case of very expressive loss of sodium and water[7]. If there is severe hypomagnesemia, this should be the first to be corrected as it has a kaliuretic effect[2].

Given the above, the aim of this case report is to communicate current knowledge about BS, in order to enable its inclusion as a differential diagnosis in the face of suspicious signs. Thus, an early therapeutic approach minimizes the biopsychosocial impact on the family nucleus involved and can restore the pace of growth of the pediatric patient.

CASE REPORT

Male patient, 2 years and 8 months old, being seen by the otorhinolaryngology staff for congenital bilateral sensorineural hearing loss, referred to pediatrics for investigation of polydipsia and polyuria, noticed by parents since approximately 1 year and 6 months of age.

The mother reported that she noticed the beginning of the craving for water when the child started to refuse food, both in quantity and variety, replacing meals with liquid. The patient's daily water intake was approximately 20 cups a day, associated with 3 nocturnal awakenings with thirst. In addition, the mother reported episodes in which the child ingested non-potable liquids, such as water for cleaning the house; and numerous diaper changes due to profuse diuresis. She denied the presence of fever, polyphagia, asthenia, vomiting, abdominal pain and dyspnea.

The physical examination at the pediatric appointment showed a weight of 8.445 kilograms (kg) (low weight for age), head circumference of 48 centimeters (cm) (appropriate for age), height of 83 cm (appropriate length for age) and BMI of 12. 3 kg/meter² (accentuated weight loss). Other findings were speech delay, delay in neuropsychomotor development (she still couldn't walk) and triangular face with broad forehead, sunken eyes and prominent ears.

The mother's gestational history revealed an uninvestigated polyhydramnios during pregnancy, premature delivery via cesarean section with no apparent cause at 33 weeks of gestation, and non-consanguineous parents.

At birth, the patient's weight was 1990 grams, classifying him as appropriate for gestational age and low weight; height, 45 cm; head circumference, 32 cm; and Apgar score, 6 and 7, in the first and fifth minutes, respectively. The patient showed significant respiratory distress at birth, requiring the use of CPAP for 48 hours and admission to the neonatal intensive care unit. Furthermore, he evolved with jaundice requiring phototherapy. He was discharged from the hospital after 29 days.

When screening the newborn, alterations were detected in the evoked otoacoustic emissions test ("little ear test") and, after further investigation by otorhinolaryngology staff, congenital bilateral sensorineural hearing loss was diagnosed.

Given the clinical picture, the following diagnostic hypotheses were suggested: nephrogenic diabetes insipidus, renal tubular acidosis and chronic malnutrition secondary to tubulopathy. Water balance, venous blood gas analysis, electrolytes, type 1 and 24-hour urine, hand and wrist X-ray, electrocardiogram and serum renin and aldosterone levels were requested. Therefore, polyuria was confirmed, as well as the presence of metabolic alkalosis, hypokalemia, hypochloremia, alkaline urine with low density and hypercalciuria. There was no evidence of glycosuria, rickets or dental alterations.

Thus, the first two diagnostic hypotheses were excluded and, considering the alterations found in complementary exams, associated with weight and height delay and perinatal history, the clinical diagnosis of BS was suggested as the cause of tubulopathy and its pathological consequences.

COMMENTS

BS encompasses a set of renal tubular alterations, caused by mutations in six different genes, whose result is the failure in the reabsorption of sodium chloride in the thick portion of the loop of Henle[4]. Therefore, pathophysiologically, there is a slight depletion of extracellular volume and consequent activation of the renin-angiotensin-aldosterone system[3].

With the increase in the production of angiotensin II, there is an increase in cyclooxygenase-2 (COX-2) activity in the dense macula, compromising even more the urinary loss of sodium by the excessive production of prostaglandin E2 (PGE2)[7]. Still, the excess sodium intake in the distal tubular portions promotes potassium and hydrogen spoliation and the decrease in chloride reabsorption reduces the renal excretion of bicarbonate, promoting its metabolic retention[2,7]. Thus, the metabolic alterations characteristic of BS are justified.

Clinically, BS is divided into antenatal (types I, II and IV) and classic (type III) forms, which present an autosomal recessive genetic inheritance pattern[6]. The other two types of the syndrome, types V and VI, have different inheritance patterns: autosomal dominant and X-linked recessive, respectively[4].

In each type of BS, there are mutations in different genes and, therefore, the phenotypes show variations. In type I, the mutation is in the SLC12A1 gene; in type II, KCNJ1 gene; in type III, CLCNKb gene; in type V, CASR gene; and, in type VI, the CLCN5 gene[4]. In type IV, the genes involved are BSND and CLCNKa-CLCNKb, both responsible for the functionality of the CLC-Ka and CLC-Kb channels[5,6].

The compromised channels in type IV are expressed in the kidneys and inner ear and, therefore, the mutations result in the unique phenotype of type IV BS: perinatal manifestations of polyhydramnios and prematurity, congenital bilateral sensorineural hearing loss, polyuria with severe salt loss and alterations hydroelectrolytics[6]. In the case described, despite not having an apparent cause at first, the perinatal complications were important for suggesting the clinical diagnosis of BS, since the other alterations were noticed later.

Thus, the signs and symptoms presented by the patient are suggestive of type IV BS: congenital bilateral sensorineural hearing loss and metabolic alterations, associated with polydipsia, polyuria, delay in growth and development and typical facies. These findings are in line with other cases described in the literature of patients with the same genetic mutation (p.G47R)[8]. However, in the reported case, early-onset nephrocalcinosis was also found in the ultrasonography of the kidneys and urinary tract, a more frequent complication in other types of BS[2].

Subsequently, for the definitive diagnosis, genetic tests were performed, which revealed a homozygous p.G47R mutation in the BSND gene. There are at least thirteen possible mutations in this gene, of variable severity, with the p.G47R mutation, classified as missense mutation, related to milder renal phenotypes[8].

The therapy was started as soon as the clinical diagnosis was made, using the treatment recommended by the current literature: potassium chloride supplementation and use of indomethacin. The use of hydrochlorothiazide was also started, with good tolerance and acceptance of the drugs. Also, the patient received a unilateral cochlear implant in the left ear at 19 months, with subsequent follow-up by speech therapy. Also noteworthy is the genetic counseling carried out with those responsible, which culminated in the decision to have tubal ligation.

In BS, the curative treatment of the primary tubular defect is achieved only through renal transplantation; however, correct adherence to clinical treatment throughout life guarantees a good prognosis[2]. Resumption of growth and development is expected even in cases associated with severe malnutrition, as reported, although the pace is slower. Furthermore, in the case in question, because it is type IV BS and because it is associated with nephrocalcinosis, there is a greater risk of developing chronic kidney disease in the long term[6].

We also stress the economic impact for the family and for the healthcare system, since patients with this disease are susceptible to frequent volume imbalances, electrolyte and acid-base disorders, culminating in repeated hospitalizations. There is also a need for close and careful multidisciplinary outpatient follow-up, associated with frequent monitoring of laboratory tests and nutritional status.

Thus, despite being a chronic disease, with non-curative treatment, the inclusion of BS as a differential diagnosis in patients with suggestive clinical signs is of unique importance, since effective management aims at recovery and optimization of weight and height gain, in addition to allowing adequate neuropsychomotor development.

Therefore, the importance of early diagnosis with adequate treatment and follow-up is highlighted as the main means of preventing a poor and irreversible prognosis for the development and growth of pediatric patients. In addition, multidisciplinary follow-up (pediatrics, genetic counseling, speech therapy and nephrology) may enable a better quality of life for the patient.

REFERENCES

1. Rudin A. Bartter's syndrome. A review of 28 patients followed for 10 years. Acta Med Scand. 1988;224(2):165–71.
2. Emmett M, Ellison DH. Bartter and Gitelman syndromes. In: Post TW, editor. UpToDate. Waltham, MA: UpToDate; 2020.
3. Bokhari SRA, Zulfiqar H, Mansur A. Bartter Syndrome. In: StatPearls [Internet]. StatPearls Publishing; 2020.
4. Howles SA, Thakker RV. Genetics of kidney stone disease. Nat Rev Urol [Internet]. 2020 Jun 12; Available from: http://dx.doi.org/10.1038/s41585-020-0332-x
5. Li J, Hu S, Nie Y, Wang R, Tan M, Li H, et al. A novel compound heterozygous KCNJ1 gene mutation presenting as late-onset Bartter syndrome: Case report. Medicine . 2019 Aug;98(34):e16738.
6. Fulchiero R, Seo-Mayer P. Bartter Syndrome and Gitelman Syndrome. Pediatr Clin North Am. 2019 Feb;66(1):121–34.
7. Mrad FCC, Soares SBM, de Menezes Silva LAW, dos Anjos Menezes PV, Simões-e-Silva AC. Bartter's syndrome: clinical findings, genetic causes and therapeutic approach [Internet]. World Journal of Pediatrics. 2020. Available from: http://dx.doi.org/10.1007/s12519-020-00370-4
8. Lee HS, Cheong HI, Ki C-S. A case of antenatal Bartter syndrome with sensorineural deafness. J Pediatr Endocrinol Metab. 2010 Oct;23(10):1077–81.