Bartter syndrome: Case report

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ABSTRACT

Bartter's syndrome (BS) is a rare group of autosomal recessive diseases of the renal tubules, causing extensive salt elimination. It is classified into 5 types, based on genotype and phenotypic manifestations. A 24-year-old male patient reports growth failure, cramps, muscle weakness and leg pain since childhood with clinical worsening in recent years, making it impossible to walk. Laboratory tests: K 1.9 mmol/L; Mg 2.49 mg/dL; PTH 12.6 pg/mL; vitamin D 76.4 ng/mL; calcium 10.1mg/dL; renin 29.32 ng/mL/h; aldosterone 19.4 ng/dL. After the initiation of Aldactone 300mg/day, there was clinical and laboratory improvement. The patient was under outpatient follow-up. The diagnosis of BS is based on clinical findings, biochemical findings, and sonographic findings. Classical pharmacological therapy includes chloride supplementation, indomethacin protaglandin inhibitors, and aldosterone spironolactones antagonists. The in-depth understanding of the pathophysiology of these syndromes, facilitated by molecular diagnosis, highlights the importance of continuous study of these conditions for the development of more effective therapeutic strategies.

Keywords: Bartter's syndrome, Metabolic alkalosis, Growth retardation.

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INTRODUCTION

Bartter's syndrome (BS) is a rare group of autosomal recessive diseases of the renal tubules, causing extensive salt elimination. It is characterized by significant metabolic alterations such as hypocalcemic metabolic alkalosis associated with hyperreninemic hyperaldosteronism in normotensive people, with juxtaglomerular hyperplasia seen on renal biopsy. There is no predilection for gender or race, and it is usually diagnosed in childhood or adolescence (Qasba et al., 2023).

The clinical picture of BS is recognized as polyuria, polydipsia, growth retardation, vomiting, dehydration, and recurrent fever simultaneously with electrolyte disturbances, which can lead to neurological changes such as areflexia, seizures, even quadriparesis or respiratory difficulty depending on the severity of the alteration of circulating minerals in the body (Wander, 2023).

BS can manifest before birth, and is called antenatal, and is usually severe. The classic form of the disease, on the other hand, begins in childhood and is usually milder. BS is classified into 5 types, which are based on genotype and phenotypic manifestations. Although all subtypes are related to problems in salt reabsorption along the ascending portion of the loop of Henle, some genotypes overlap, with molecular patterns associated with certain genes (FREMONT et al., 2012; RAVAROTTO et al., 2022).

Type I, caused by mutation in the SLC12A1 gene, affects the Na-K-Cl co-transporter, formerly known as antenatal SB or hyperprostaglandin E syndrome. Type 2, also known as antenatal SB, is associated with a mutation in the KCNJ1 gene, which affects potassium-regulating ROMK channels, which are associated with preterm births and severe dehydration. Type 3 results from mutation of the CLCNKB gene, giving rise to a defective chloride channel. It is associated with milder symptoms. Type 4 is related to mutation of the BSND gene, and is related to sensorineural deafness, severe salt loss, premature births, and polyhydramnios. Type 5 is associated with mutation in the CASR gene, with an X-linked recessive inheritance pattern, leading to hypercalciuria (FREMONT et al., 2012; RAVAROTTO et al., 2022).

Treatment options for BS include salt supplementation, NSAIDs, and aldosterone antagonists. Procedures such as amniocentesis and indomethacin therapy have been shown to be effective. Due to the rare and recent nature of this pathology, treatment options are still limited, and symptoms must be controlled, since there is no cure. The information provided by the literature on this syndrome is still scarce (Qasba et al., 2023). Therefore, the objective of this study is to report a case of a patient with a recent diagnosis of BS.

CASE REPORT

A 24-year-old male patient reports growth failure, cramps, muscle weakness and leg pain since childhood with clinical worsening in recent years, making it impossible to walk. Patient

complaining of enuresis. On physical examination: systemic blood pressure: 107x89 mmHg, heart rate: 81 beats per minute, absence of edema. Laboratory tests: K 1.9 mmol/L; Mg 2.49 mg/dL; PTH 12.6 pg/mL; vitamin D 76.4 ng/mL; Calcium 10.1mg/dL; Renin 29.32 ng/mL/h; Aldosterone 19.4 ng/dL. A CT scan of the total abdomen showed gross calcifications in the right adrenal gland. After the initiation of Aldactone 300mg/day, there was clinical and laboratory improvement. The patient was under outpatient follow-up.

DISCUSSION

BS is a rare autosomal recessive condition that results in tubulopathies that lead to impaired transport mechanisms. As a consequence, there is a decrease in sodium absorption in the ascending loop of Henle, activation of the renin-angiotensin-aldosterone system, with consequent hypokalemic and hypochloremic metabolic alkalosis, and alteration in the feedback mechanism at the level of the macula densa in cases of hypovolemia. With this physiological change, there is an increase in the production of prostaglandins that stimulate renin secretion and aldosterone production, in an attempt to reestablish glomerular perfusion through normalization of intravascular volume. As chloride is not being reabsorbed into the macula densa, tubuloglomerular feedback does not occur, and prostaglandins are continuously produced by cells, leading to excessive renin-aldosterone synthesis (Fremont et al., 2012; KONRAD et al., 2021).

Deficient salt reabsorption in the ascending branch of the loop of Henle leads to consequences that characterize the clinical practice of BS. As a first consequence, there is a reduction in calcium reabsorption, thus we can infer a picture of hypercalciuria and progressive medullary nephrocalcinosis. The second consequence is the reduction of the osmotic gradient in the renal medulla, causing isosthenuria, i.e., impaired ability to dilute or concentrate urine. With the exception of patients with type 3 SB, who do not have hypercalciuria and have the partial ability to concentrate urine. In addition to the above, the clinical picture observed includes a history of polyhydramnios with prematurity, growth retardation, increased pH, low blood pressure or within the normal range (FREMONT et al., 2012; KONRAD et al., 2021; SUPRIYANI et al., 2023).

Like BS, Gitelman's syndrome (GS) also results from birth defects in the tubular filtration of sodium, chloride and potassium. GS, also known as familial hypocalcemia-hypomagnesemia, is an autosomal recessive inherited disease characterized by dysfunction in salt reabsorption in the distal convoluted tubule (DCT), presenting clinically as a pseudo-Bartter syndrome. Symptoms usually begin after 6 years of age, but may manifest late, during adolescence or adulthood (ALLA et al., 2023; CUNHA et al., 2018; FULCHIERO et al., 2019).

OS is caused by mutations in the SLC12A3 gene, encoding the thiazide-sensitive sodium chloride (NaCl) cotransporter (NCC) in the distal convoluted tubule (TCD). This mutation results in

the inactivation of the gene and consequently reduces the reuptake of NaCl by the affected cells, triggering a cell contraction and cascade stimulation of the renin-angiotensin-aldosterone system (RAAS) (FULCHIERO et al., 2019).

The characteristic clinical signs of GS include hypokalemia, metabolic alkalosis, hypocalciuria, and hypomagnesemia, commonly accompanied by symptoms such as salt cravings, fatigue, muscle weakness, cramps, palpitations, and nocturia. The differentiation between OS and BS is based on clinical criteria, including early age of onset, severity of symptoms, presence of hypercalciuria, polyhydramnios, in cases of BS. However, recent advances in medical understanding have revealed that patients with BS may manifest later and develop additional complications, such as growth retardation and developmental delay (CUNHA et al., 2018; FULCHIERO et al., 2019; KONRAD et al., 2021).

The following table demonstrates the molecular differences and clinical features between Bartter's syndrome and Gitelman's syndrome.

Table 1: Genetic and clinical findings of Bartter's Syndrome and Gitelman's Syndrome

	Produto genético	Mutação genética Herança da banda cromossômica/OMIM Características clínicas			
Síndrome de Bartter (apelido)					
Tipo 1 (síndrome de Bartter pré-natal; síndrome de hiperprostaglandina E)	NKCC2	SLC12A1	15q21.1	AR/601678	polidrâmnio, prematuridade, poliúria, nefrocalcinose
Tipo 2 (síndrome de Bartter neonatal com hipercalemia transitória; síndrome de hiperprostaglandina E)	ROMA	KCNJ1	11q24.3	AR/241200	polidrâmnio, prematuridade, poliúria, nefrocalcinose, hipercalemia transitória acidose
Tipo 3 (síndrome de Bartter clássica)	ClC-Kb	CLCNKB	1p36.13	AR; muitos são esporádico/607364	Nascimento a termo, sem nefrocalcinose
Tipo 4 (síndrome de Bartter pré-natal; síndrome de hiperprostaglandina E com surdez neurossensorial, BART)	Barttin (subunidade b de ClC-Ka e ClC-Kb)	BSND	1q32.3	AR/602522; digênico em CLCNKA e Genes CLCNKB	Prematuridade, surdez neurossensorial, sem nefrocalcinose
Tipo 5 (hipocalcemia com Síndrome semelhante a Bartter)	CASR	L125P	3q21.1	AD/601199	Hipocalcemia, PTH suprimido
Síndrome de Gitelman	NCCT	SLC12A3	16q13	AR/263800	Hipocalciúria, hipermagnesiúria e hipomagnesemia

NKCC2: cotransportador Na-K-Cl sensível à furosemida; ROMK: canal de K medular externo renal; ClC-Kb: canal de cloreto-Kb; ClC-Ka: canal de cloreto-Ka; CASR: receptor sensível ao cálcio; NCCT: cotransportador de NaCl sensível a tiazidas; AR: autossômico recessivo; DA: autossômica dominante; OMIM: Herança Mendeliana Online no Homem; PTH: hormônio da paratireóide.

Fonte: Fremont *et al.* (2012)

Regarding the diagnosis of BS, it is based on clinical findings, biochemical findings, and sonographic findings. In this analysis, the suspicion of BS, already in the gestational period, occurs in situations of prolidramnios. At this juncture, there are two possibilities for confirming the diagnosis: prenatal genetic testing and biochemical analysis of the amniotic fluid. In both cases, there are high risks of gestational complications, since the methods mentioned above are invasive (FULCHIERO et al., 2019; KONRAD et al., 2021; QASBA et al., 2023).

In order to distinguish between OS and BS, it is important to observe the presence of calcium in the urine, since in OS there is hypocalciuria and in BS there is hypercalciuria. Calcium imbalance is associated with arthropathy with deposition of calcium pyrophosphate crystals or

chondrocalcinosis. In addition to this alteration, there are changes in the electrocardiogram with prolongation of the QT interval, causing arrhythmias. (RAVAROTTO et al., 2022; SUPRIYANI et al., 2023).

As a rule, most cases of BS present with delayed and failed growth in individuals with the syndrome. In addition, early labor and polyhydramnios are recurrent. Diarrhoea, vomiting and fever are reported. From another perspective, that of physical characteristics, individuals with Bartter have a prominent forehead, triangular face, protruding tongue, enlarged eyes and auricle. However, it is indicated that the diagnosis should be made from a genetic approach due to the similarity of the phenotype presented with other diseases, including GS (CUNHA et al., 2018; FULCHIERO et al., 2019; KONRAD et al., 2021).

In addition, the thiazide test is proposed to help distinguish between BS and OS and involves the oral administration of hydrochlorothiazides, 1 mg/kg up to 50 mg, and after 7 days, with the suspension of all medications, except potassium and magnesium. In patients with GS, there is a slight change in chloride excretion due to the mutation in NCCT cotransporters. In contrast, patients with BS have a limitation in response to hydrochlorothiazides and an increase in chloride excretion. However, the high risk of blood volume depletion in this diagnostic strategy is recognized (KONRAD et al., 2021; QASBA et al., 2023).

It is also meritorious to pay attention to the conditions that simulate BS, i.e., pseudo-SBs. In this analysis, nephrotoxic agents, such as aminoglycosides, amphotericin B, and heavy metals, are associated with the BS phenotype. Added to this knowledge are congenital chloride diarrhea and cystic fibrosis, both characterized, each in its own way, by the loss of sodium chloride. It is also part of the falsification of the diagnosis of BS in situations in which patients suffer from bulimia and in those who abuse diuretics (FULCHIERO et al., 2019; KONRAD et al., 2021; QASBA et al., 2023).

The limitation of BS treatment is related to its rarity. In this scope, the therapeutic approach varies comprehensively among health professionals, who report specificities of each case and their individual experiences. However, classical pharmacological therapy includes chloride supplementation, protaglandin inhibitors indomethacin and aldosterone antagonists spironolactones. In prenatal cases, the use of amniocentesis is recommended to prolong pregnancy, although it has not been evaluated in prospective studies. (CUNHA et al., 2018; (FULCHIERO et al., 2019; KONRAD et al., 2021; QASBA et al., 2023).

Potassium supplementation is also added, although it is not widely tolerated in high doses. Therefore, potassium-sparing diuretics are chosen to help increase serum potassium and reverse metabolic alkalosis (FULCHIERO et al., 2019; KONRAD et al., 2021; QASBA et al., 2023).

It is worth noting that angiotensin-converting enzyme inhibitors can be used in cases of proteinuria to correct the low concentration of potassium ion. However, due to polyuria and

symptoms of dehydration, there is a need for caution in the use of the drugs mentioned above due to the potential risk of kidney damage. In short, such therapy can lead to an improvement in the growth of the stability of metabolic and serum levels of depleted ions (FULCHIERO et al., 2019; KONRAD et al., 2021; QASBA et al., 2023).

It is also important to point out the existence of possible gastrointestinal involvements, which are severe and frequent in patients who use prostaglandins for an extended time. Due to this understanding, it is necessary that routine endoscopies be applied to patients who are treated with the aforementioned pharmacological group (FULCHIERO et al., 2019).

It is imperative to identify the development of foci of Focal Glomerulosclerosis (GF) during the course of SB. In this sense, according to the physiological mechanism of the disease, consistent stimulation of the renin-angiotensin axis causes secondary glomerular hyperfiltration. In such a situation, although little reported, the consequent renal failure, suggested by the progress of FG, is addressed with transplantation of the organ in question (FULCHIERO et al., 2019).

Osteopenia is also present in BS patients, probably due to the manifestation of the hypercalciuric phenotype. Therefore, bone mineral density should be monitored in patients with BS. In addition, in cases where there is failure in body growth, or short stature, the use of Growth Hormone (GH) is recommended, although in previous studies, the use of GH has been shown to be ineffective in patients with severe hypokalemia (FULCHIERO et al., 2019).

The prognosis in individuals with BS is satisfactory after a therapeutic follow-up of at least 10 years, which does not exclude the onset of late manifestations of the disease, such as proteinuria and renal failure (QASBA et al., 2023).

CONCLUSION

Based on the data presented, we can conclude that BS, although rare, represents a significant challenge in diagnosis and clinical management, especially in neonates. The in-depth understanding of the pathophysiology of these syndromes, facilitated by molecular diagnosis, highlights the importance of continuous study of these conditions for the development of more effective therapeutic strategies. In addition, chronic hypokalemia, associated with BS and GS, requires careful attention, as it can lead to serious complications such as rhabdomyolysis and cardiac arrhythmias. Physicians' awareness of these tubular renal congenital disorders is critical for proper treatment and to avoid serious complications.

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