

## Bartter syndrome: an infrequent tubulopathy of prenatal onset

### Síndrome de Bartter: una tubulopatía infrecuente de inicio antenatal

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#### Abstract

**Introduction:** Bartter syndrome (BS) is a rare inherited tubulopathy that has two presentation forms, the first one is a severe form of antenatal onset (neonatal Bartter) and the second one is a later onset form during the first years of life (classic Bartter). In the antenatal form, it manifests with fetal polyuria, polyhydramnios of early and severe onset, premature delivery, and intrauterine growth restriction. In the postnatal stage, it presents recurrent episodes of dehydration and electrolyte imbalance that can compromise the survival of the patient. **Objective:** To report a clinical case of neonatal BS and a review of the literature. **Clinical Case:** Premature newborn of 35 weeks of gestation with history of severe polyhydramnios diagnosed at 27 weeks of gestation, without apparent cause. From birth, the patient presented polyuria and hypokalemic metabolic alkalosis making a diagnosis of Neonatal Bartter Syndrome in the first week of life. Laboratory tests confirmed urinary electrolyte losses. The patient was treated with strict water balance and sodium and potassium supplementation, achieving weight and electrolyte imbalance stabilization. The patient remains in control in the nephrology unit, with potassium gluconate and sodium chloride supplementation. At the fourth month, ibuprofen was added as part of treatment. At the seventh month of life, renal ultrasound showed nephrocalcinosis. At one year of life, profound sensorineural hearing loss was observed requiring a cochlear implant. **Conclusion:** The presence of severe polyhydramnios of early onset with no identified cause should lead to suspicion of neonatal BS which even when infrequent determines severe hydroelectrolytic alterations and should be treated early.

#### Keywords:

Bartter syndrome;  
polyhydramnios;  
hypokalemic metabolic  
alkalosis;  
tubulopathy

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## Introduction

Bartter Syndrome (BS) is a rare, inherited tubulopathy that has two forms of presentation, a severe one of antenatal onset (neonatal Bartter) and one of later onset, during the early years of life (classic Bartter). This syndrome is part of a genetically heterogeneous and infrequent group of entities defined by abnormalities in the renal tubular function that are inherited in an autosomal recessive pattern. The primary pathogenic mechanism is the defect in sodium and chloride reabsorption in the thick ascending limb of the loop of Henle (TALH).

It was described in the '60s by Bartter et al.<sup>1</sup> who reported salt-losing nephropathy characterized by hypokalemia, metabolic alkalosis, polyuria, and juxtaglomerular apparatus hypertrophy. Advances in genetics and molecular biology allowed us to know that it is a heterogeneous genetic disorder caused by a defect in sodium, chlorine, and potassium reabsorption in the TALH.

It is characterized by polyuria associated with hypokalemia, hypochloremia, metabolic alkalosis, hypercalciuria, and secondary hyperreninemic hyperaldosteronism with normal or low blood pressure<sup>1</sup>.

Although seven genetic variants have been described, only two clinical forms of the disease are distinguished. A form of prenatal onset characterized by polyhydramnios and premature birth, with the neonate presenting severe dehydration due to polyuria in the first days of life, evolving early with nephrocalcinosis, and characteristic biochemical alterations (neonatal BS), and a less severe form called classical BS of later onset, usually in the first two years of life, with growth deficit and recurrent episodes of dehydration<sup>2-3</sup>. The exact incidence of BS is unknown, but it is estimated in 1.2/1,000,000 birth<sup>4</sup>. The objective is to report a clinical case of a patient with neonatal BS and to present a review of the pathology.

## Clinical Case

Female newborn, second child of non-consanguineous parents. The mother was 26 years old, healthy, referred to maternity at 27 weeks due to severe polyhydramnios with amniotic fluid index (AFI) 41.7, where AFI > 24 is a polyhydramnios indicator and > 40 indicates severe polyhydramnios. Fetal malformations, maternal diabetes, and placental pathology are ruled out. At 35 weeks of pregnancy, the mother presented AFI 54. Due to deterioration of the fetoplacental unit, the child born by cesarean section at 35 weeks, Apgar 9-9, weight 2,180 grams, and height

47 cms. She presented normal muscle tone and no dysmorphism. Esophageal atresia was ruled out. She evolved with difficulty breathing with low oxygen requirements.

The patient presented early significant polyuria (7.1 ml/kg/h). At 24 hours of life, she presented natremia 136 mEq/l, kalemia 4.0 mEq/l, hypochloremia 89 mEq/l, metabolic alkalosis pH 7.45, and bicarbonate 27.2 mmol/l. Weight loss was 6% after 24 hours, accentuating until reaching a drop of 19% on the 10th day. She was managed with fluid intake between 150-184 ml/kg/day, sodium up to 7.6 mEq/kg/day, and potassium 3.6 mEq/kg/day.

The patient evolved with tendency to hyponatremia, hypochloremia, and hypokalemic metabolic alkalosis (pH 7.47; bicarbonate 30 mmol/l; sodium 123 mEq/l; potassium 2.2 mEq/l; chlorine 75 mEq/l). Calcium, magnesium, urea nitrogen, and creatinemia were in normal ranges as well as blood pressure.

On the 5th day, the patient presented elevated urinary sodium (FeNa 25%) and potassium (Fe K 32.4%) losses. Urine calcium-creatinine ratio of 0.99 (Normal for age < 0.8).

Considering the clinical and laboratory evolution, a diagnosis of neonatal BS was proposed. She was managed with strict fluid balance, sodium 6.5 to 7.6 mEq/kg/day and potassium 3 to 3.6 mEq/kg/day contributions, managing to stabilize weight and electrolytes, maintaining diuresis between 3-5 ml/kg/h. On the 18th day, she achieved exclusive oral intake and enteral supplementation of sodium and potassium was maintained, well tolerated. The patient regained birth weight by the 20th day of life.

Renal ultrasound on the fifth day was normal, however, when repeating it at 27 days, it shows a thin hyperechoic rim in the pyramids suggestive of nephrocalcinosis. BERA hearing screening was normal at 3rd day of life.

She was discharged at 35 days, with indication of oral supplementation of NaCl 6.4 mEq/kg/day and potassium gluconate 3.1 mEq/kg/day.

The patient continued in follow-up in Nephrology, with supplementation of potassium gluconate, which had to be increased from 2 to 3 mEq/kg/day at three months due to a tendency to hypokalemia. Normal natremia with sodium chloride contributions of 3.8 mEq/kg/day. She presented metabolic alkalosis, bicarbonate of 31.6 mmol/l. Ibuprofen was added in the fourth month. She evolved with slow weight and height progress and hypotonia. Nutritional evaluation at the 6th month confirmed moderate chronic malnutrition. Renal ultrasound at the 7th month reveals nephrocalcinosis. At one year of age, profound sensorineural hearing loss was observed requiring a cochlear implant.

## Discussion

Mutations of several genes encoding the transporters involved in the reabsorption of salt in the TALH cause different types of BS that are classified according to the genetic alterations involved (Table 1). Type I or antenatal BS, formerly known as Hyperprostaglandin E Syndrome caused by mutation of the SLC12A1 gene on chromosome 15q15-21<sup>5,6</sup> encoding the furosemide-sensitive Na-K-2Cl cotransporter (NKCC2) in the renal tubule and responsible for the reabsorption of about 30% of filtered NaCl. These biochemical abnormalities are similar to those induced by chronic furosemide therapy.

BS type II also called along with the type I, antenatal BS, has a KCNJ1 gene mutation that encodes ROMK channel, which recycles and reabsorbs potassium into the tubular lumen<sup>7</sup>. When the ability to recycle potassium from cells into tubular lumen is lost, the luminal potassium concentration is too low to allow the activity of the Na-K-2Cl cotransporter. This potassium channel (ROMK) is also expressed in cells of the collecting tubule and these patients may initially present transient hyperkalemia and later develop hypokalemia.

The classic BS or type III, caused by a mutation in the gene coding for chloride channel CLC-Kb located

on chromosome 1p36 has a wide phenotypic variety, can originate antenatal presentations or simulate a Gitelman syndrome with hypocalciuria and hypomagnesemia<sup>8-10</sup>. A tubular resorption reduction of NaCl is secondary to the functional defect of the chloride channel (CLC-Kb). Since there is another chloride channel on the basolateral side, CLC-Ka, the NaCl loss is likely to be lower than in neonatal variants and there will be less urine calcium excretion and less likelihood of nephrocalcinosis.

The BS type IVA, appears with severe antenatal form accompanied by sensorineural hearing loss<sup>11</sup> due to the BSND gene mutation that encodes for Barttin protein, essential for the correct functioning of chloride channels CLC-Ka and CLC Kb, which are found in the basolateral membrane of renal tubules and also in the epithelium secreting potassium from the inner ear, thus the mutation of this gene also produces an inability to secrete potassium inside the endolymph, which explains the auditory impairment.

An additional subtype of BS with sensorineural hearing loss has been reported that does not present mutation in the gene coding for Barttin protein but does present heterozygous mutations (digenic inheritance) in the two genes coding for the chloride channels CLC-Ka and CLC Kb that has been denominated BS type IVB<sup>12</sup>.

**Table 1. Characteristics of the different types of Bartter syndrome**

Type	Gen involved	Co-transported protein affected	Type of genetic transmission	Polyhydramnios	Clinical presentation
Bartter type I	SLC12A1	NKCC2	Autosomal recessive	Very frequent	Antenatal presentation. Polyuria, hypochloremia, hypokalemia, metabolic alkalosis, nephrocalcinosis
Bartter type II	KCNJ1	ROMK	Autosomal recessive	Very frequent	Antenatal presentation. Initial transient hyperkalemia (66% of cases), subsequent hypokalemia. Polyuria, hypochloremia, metabolic alkalosis, nephrocalcinosis
Bartter type III	CLC-Kb	CLC-Kb	Autosomal recessive	Infrecuente	Presentation 0-5 years (Classic or antenatal). Hypochloremia, hypokalemia, metabolic alkalosis. Hypomagnesemia Great clinical variability. Infrequent nephrocalcinosis
Bartter type IVA	BSND	Barttin	Autosomal recessive	Very frequent	Antenatal presentation. Polyuria, hypochloremia, hypokalemia, metabolic alkalosis. Sensorineural deafness. Infrequent nephrocalcinosis
Bartter type IVB	CLC-Ka y CLC-Kb	CLC-Ka y CLC-Kb	Autosomal recessive. Digenic		
Bartter type V	CaSR	CaSR	Autosomal dominant.	Not present	Bartter syndrome with hypocalcemia, hypokalemia, hypomagnesemia, nephrocalcinosis. Hypoparathyroidism
Bartter Transitory	MAGE-D2	MAGE-D2	Linked X chromosome, recessive	Present	Antenatal presentation. Polyuria. Transient hydroelectrolytic alterations

The BS type V, the only one of autosomal dominant inheritance, caused by gain-of-function mutations in the CASR gene coding for the calcium-sensitive receptor in the basolateral cells membrane of the TALH. It is not associated with antenatal BS<sup>13</sup>. In 2016, Laghmani described the mutation due to function loss of the MAGED2 gene, associated with a severe but transient form of X-linked antenatal BS (OMIM 300971)<sup>14</sup>. Figure 1 schematizes the disorders involved in the different types of BS.

Under physiological conditions, the ions reabsorption in the TALH is an extremely complex process that requires indemnity of the different channels and co-transporters in the tubular cell. Any defect in any of them causes renal loss of sodium, chlorine, potassium, and calcium that will try to compensate in other segments of the tubule. The earliest manifestation of this tubular dysfunction is fetal polyuria, which leads in the last trimester of pregnancy to the development of severe polyhydramnios.

Antenatal diagnosis is possible through documentation of elevated chlorine levels in amniotic fluid and genetic study<sup>15</sup>.

The direct consequence of the molecular defect in the TALH is a reabsorption failure of filtered sodium. The high amount of sodium reaching the distal nephron of the tubules exceeds the possibility of compensation for the distal convoluted tubule and the collecting ducts causing sodium loss. The chronic loss of sodium leads to contraction of the extracellular volume and secondary hypovolemia, with activation of the renin-angiotensin-aldosterone system that stimulates the sodium reabsorption in the main cell of the collecting ducts, which is accompanied by excretion of potassium and hydrogen causing hypokalemic metabolic alkalosis. The NKCC2 transporter, as well as the ROMK potassium channel, are also expressed in the macula densa and the deficiency will alter the salts detection in the tubular filtrate. This worsens a hyperreninemic state already stimulated by salt loss and volume contraction.

Prostaglandin E2 is released in response to impaired sodium absorption in the TALH and it is possible to find high levels in urine and blood, but the way it aggravates the salt and water loss of the kidneys is not completely resolved. Prostaglandin synthesis inhibi-

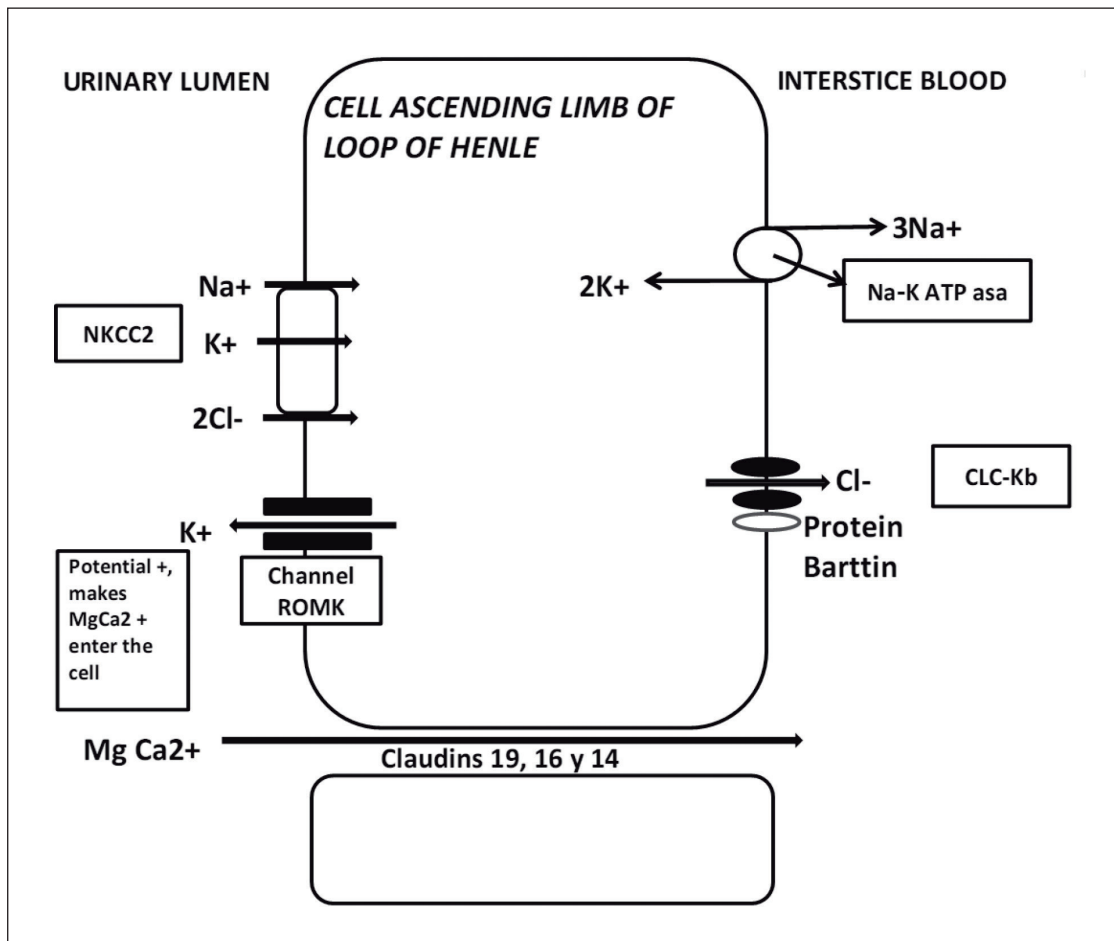


Figure 1. RAG cell of Henle's Handle. Co-transporters affected.

tors are effective in suppressing the salt and water loss and allow in affected children often achieving normal growth rates<sup>16, 17, 18</sup>.

The hypercalciuria association is explained because around 25% of filtered calcium is reabsorbed in the TALH coupled to the activity of NKCC2. The paracellular calcium reabsorption is moved by a lumen-positive transepithelial potential. There are two prerequisites for generating this transepithelial potential gradient: 1) an important transepithelial NaCl gradient dependent on the coordinated action of the Na-K-2Cl (NKCC2) cotransporter, the potassium channel ROMK, both in the apical membrane, and the chloride channel (ClCKb-barttin) in the basolateral membrane; 2) a cation-selective paracellular channel dependent on the interaction of claudin 16, 19 and 14<sup>19</sup>. The transtubular potential abolition caused by the defect in the cotransporters results in the inability to passively drive cations through the intercellular space in the loop of Henle (Fig 1).

In BS, despite having hyperaldosteronism, blood pressure is normal due to hypovolemia and elevated PGE2 levels.

Considering the pathophysiology of BS, prostaglandin synthesis inhibition at a renal and systemic level due to non-steroidal anti-inflammatory drugs is fundamental for disease control.

The use of indomethacin in the antenatal stage has been described for the management of polyhydramnios before 32 weeks of pregnancy, but its effects on ductal closure with postnatal pulmonary hypertension risk requiring strict monitoring should be considered<sup>20</sup>.

In the postnatal stage, prostaglandin synthesis inhibitors contribute to decrease polyuria, increase serum potassium, reduce hypercalciuria, but do not prevent nephrocalcinosis<sup>21</sup>.

Selective COX-2 inhibitors have proven to be as effective as the non-selective ones in reducing polyuria in antenatal BS<sup>22</sup>. However, there is not enough experience with the use of these drugs in the neonatal stage. Careful correction of the hydroelectrolytic imbalance is the fundamental aspect of management in these patients<sup>23</sup>.

In our case, the diagnosis was based on a history of severe polyhydramnios and in the postnatal stage by the presence of polyuria and hydroelectrolytic alterations with severe hypokalemia, persistent metabolic alkalosis, and nephrocalcinosis. The deep sensorineu-

ral hearing loss, in this case, would suggest BS type IV. The genetic study was not available in our case due to economic limitations. Considering the physiopathology of BS, an essential element of pre and postnatal management is the prostaglandins synthesis inhibition at renal and systemic level with non-steroidal anti-inflammatory drugs.

## Conclusion

Presence of severe early-onset polyhydramnios with no usual cause such as maternal diabetes or fetal gastrointestinal anomaly should lead to suspicion of BS, which even when infrequent, results in severe neonatal hydroelectrolytic disturbances.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors state that the information has been obtained anonymously from previous data, therefore, Research Ethics Committee, in its discretion, has exempted from obtaining an informed consent, which is recorded in the respective form

## Financial Disclosure

Authors state that no economic support has been associated with the present study.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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