



Bartter Syndrome in Children; A Cause of Severe Hypokalemic Metabolic Alkalosis: Clinical Case Report and Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. Author AR and MA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Bartter syndrome is an inherited renal tubular disorder caused by a defective salt reabsorption in the thick ascending limb of loop of Henle. It is characterized by urinary loss of sodium, potassium, and chloride; hypokalemic metabolic alkalosis; normal blood pressure, high plasma levels of renin and aldosterone. There is phenotypical and genetic variability of Bartter syndrome since we have identified five genes responsible for five different forms of Bartter syndrome. The objective of this work is to report a clinical case to study the pathophysiological, clinical, biological and therapeutic features of this syndrome.

Materials and Methods: We reported a case of 04-month-old male infant admitted for acute dehydration secondary to polyuro-polydipsia syndrome and vomiting. In clinical presentation the patient had a dysmorphic syndrome with triangular face, protruding ears and flattened nasal root. Laboratory tests revealed hypokalemia, hyponatremia, metabolic alkalosis and hypercalciuria. Treatment with indomethacin was started at 1 mg/kg per day with favorable outcome.

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1. INTRODUCTION

Bartter Syndrome (BS) is a rare genetic, autosomal recessive, renal tubular disease. It was described in the '60s by Bartter et al.1. who reported salt-losing nephropathy, characterized by hypokalemia, metabolic alkalosis, polyuria, and juxtaglomerular apparatus hypertrophy. The diagnosis is usually made in childhood in the face of a staturponderal delay, a polyuropolydipsia syndrome and digestive disorders. An antenatal form has been described, which is associated with hydramnios, prematurity and postnatal polyuria. The primary abnormality is a sodium reabsorption anomaly located in the Henle's and distal tubule, leading to salt loss, responsible for hyperaldosteronism, a polyuropolydipsia syndrome with risk of dehydration. 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 [1]. The exact incidence of BS is unknown, but it is estimated at 1 in 1,000,000 individuals [2]. Seven genetic variants have been described, but 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. [1] Treatment can vary widely among physicians and clinics and is based mainly on the understanding of renal physiology, reported clinical observations, and individual experiences. The classical pharmacological therapy includes potassium chloride supplementation, prostaglandin inhibitor (indomethacin), and aldosterone antagonist (spironolactone).

2. CASE REPORT

A 4-month-old male infant, 2nd of two siblings, admitted in a state of acute dehydration secondary to polyuria-polydipsia syndrome and vomiting.

In its antecedents we noted a first degree parental consanguinity; and three hospitalizations for episodes of acute

dehydration. Clinical examination on admission found: a weight at 6kg (normal), length of 56cm (normal), a cranial perimeter at 40cm (-1SD), depressed anterior fontanel, persistent skin fold, sunken and darkened eyes, triangular face, protruding ears and flattened nasal root. (Fig. 1). He also had polyuria with a diuresis of 7 cc/kg per hour. Blood pressure was 90/50 mmHg and the rest of the clinical examination was unremarkable. Laboratory test revealed: hypokalemia at 2.1 mmol/l, hyponatremia at 131 mmol/l, metabolic alkalosis with bicarbonates at 32 mmol/l; urea was 2.24 mmol/l and magnesium at 1.84 mmol/l (normal). Urinary ionogram objected hypercalciuria. Renal ultrasound revealed bilateral nephromegaly with cortical hyperechogenicity without nephrocalcinosis. In the presence of these signs and associated parental inbreeding, episodes of dehydration due to vomiting and a polyuria-polydipsia syndrome, with hypokalemic metabolic alkalosis and a hypercalciuria, the diagnostic of Bartter's syndrome was made. We completed the investigations with plasma renin and plasma angiotensin levels, which were very high. The patient benefited from infusion with saline 0.9% (20 ml/kg), intravenous hyperhydration with serum glucose 5% (150 ml/kg/day) with potassium chloride (5 meq/kg per day), sodium chloride (3 meq/kg per day). Vomiting and polyuria gradually regressed.

The control blood urea and electrolytes revealed: Kalemia at 4.9 mmol/l, natremia at 138 mmol/l, calciuria at 2.8 mg/kg per day with normal renal function. Treatment with indomethacin was started at 1 mg/kg per day, with favorable outcome.

The genetic study by molecular biology was not performed in our patient due to lack of means.

3. DISCUSSION

Bartter syndrome is a spectrum of disease inherited as autosomal recessive and characterized by hypokalemia, renal salt wasting, and metabolic alkalosis due to reduction or defect in the activity of one of several electrolytes transporters (Na, Cl, or K) in the thick ascending loop of Henle.

Fortunately, the clinical and biochemical features are quite characteristic. Consequently, in most cases, the correct diagnosis can be made and



Fig. 1. Image of a 4-month-old male with Bartter syndrome: triangular facies and protruding ears

the appropriate treatment can be initiated without genetic analysis [3]. Obviously, (symptomatic) therapy should be based on clinical and biochemical findings and not on the genotype. [4].

4. PHYSIOLOGY

In the Thick Ascending Limb of the loop of henle (TAL), the apically expressed, furosemide-sensitive sodium-potassium-2-chloride cotransporter (NKCC2) is the key player of the active Na and Cl uptake from the tubular lumen. Na is actively pumped from the TAL cell by the basolateral Na-K ATPase, whereas Cl₂ leaves the cell basolaterally via chloride channels [chloride channel, kidney a (ClC-Ka) and chloride channel, kidney b(ClC-Kb)]. The function of both chloride channels requires the b-subunit Barttin [3]. In contrast to Na⁺ and Cl₂, K_{+ is recycled through the potassium-permeable ion channel renal outer medullary K⁺ channel (ROMK) back into the tubule lumen. As a result, a positive transepithelial potential is generated which enables the active transcellular salt reabsorption}

as well as the passive paracellular transport of cations, which is especially essential for Ca²⁺ and Mg²⁺. The salt absorption of the TAL in combination with the water impermeability of this tubule segment generates the high tonicity of the interstitium and is therefore, the prerequisite for the countercurrent principle and thus the urine concentration mechanism. NKCC2 and ROMK are also expressed in the macula densa, where they play a crucial role in the specific salt sensor function of macula densa cells [5].

5. CLASSIFICATION

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 .

Type I or antenatal BS, formerly known as Hyperprostaglandin E Syndrome caused by mutation of the SLC12A1 gene on chromosome 15q15-21 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. [1].

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. 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. [1].

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. 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. [1].

The BS type IVA, appears with severe antenatal form accompanied by sensorineural hearing loss 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. [1].

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 IVB12. [1]. 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. 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) [1].

Previously, another terminology had been proposed to separate BS into "antenatal BS" (types I, II, and IV BS), associated to a more severe presentation, from "classic" BS (type III BS) with a later presentation in childhood. However, the latest findings show a wide spectrum of severity in all forms of BS: some patients with types I, II, or IV BS presenting with late-onset forms, whereas some patients with type III BS may appear with a severe antenatal presentation [6].

6. CLINICAL PRESENTATION

Antenatal Bartter Syndrome is characterized by major renal fluid and electrolyte loss, which is expressed as early as the antenatal period with severe hydramnios. Our patient had no history of hydramnios. Water loss is sometimes associated with a loss of salt. Dilation of the urinary tract, and is complicated in the neonatal period by episodes of severe dehydration. It is associated with marked hypercalciuria, generally complicated by antenatal or neonatal nephrocalcinosis, and more rarely with very early renal lithiasis [7]. Some patients have a peculiar facial appearance, with a triangular shaped face, prominent forehead, large eyes, protruding ears and droopy mouth, as is the case with our patient who presents triangular face, protruding ears and flattened nasal Root. A subtype of Bartter's syndrome is associated with sensorineural hearing loss and strabismus [7]. In the absence of hydramnios, an age of presentation before 3 years and the presence of nephrocalcinosis or hypercalciuria suggest a classic Bartter syndrome.

In infants, it is frequently discovered during digestive disorders (anorexia, diarrhea, vomiting) with dehydration, revealing nephrocalcinosis and/or renal incapacity to adapt to extrarenal fluid and electrolyte losses. Rarely, the calciuria is normal and the nephrocalcinosis is absent, suggesting a less severe form.

In the older child, the first biological examinations may be motivated by constant and severe growth retardation, polyuro-polydipsia, a slight delay of the psychomotor development, or by symptoms attributed to hypokalemia (muscle weakness, constipation and cramps) [7].

7. BIOLOGICAL SIGNS

The cardinal sign is renal loss of potassium defined by hypokalemia (less than 3.5 mmol/L) chronic (found on two independent measurements several days apart), contemporary with inappropriate kaliuresis. Inappropriate kaliuresis is classically defined by a urinary excretion of potassium greater than 40 mmol/24 h on a correct urine collection of 24 hours attested by creatinuria. This loss of potassium must be associated with at least three additional elements: the absence of acidosis, the absence of the intake of medicines capable of inducing renal loss of potassium and/or magnesium, and preserved natriuresis (greater than 20 mmol/L). In the presence of marked alkalosis ([bicarbonates] > 28 mmol/L), it is necessary to measure chloruria in order to exclude chlorinated depletion (see below). Renin is elevated, with aldosteronemia often being normal, dissociated from renin due to the inhibitory effect of hypokalemia on aldosterone secretion [7]. Our patient also had hypokalemia, hyponatremia, metabolic alkalosis and hypercalciuria and normal magnesias

8. EVOLUTION AND COMPLICATIONS

Hydramnios associated with antenatal Bartter often requires decompression amniocentesis. Early diagnosis may be guided by a history of Bartter in the siblings, or the notion of consanguinity in the parents. It allows better therapeutic management of severe neonatal hydroelectrolytic disorders that can be prevented by continuous or intermittent feeding [7]. From the second month of life, treatment with indomethacin can be introduced and generally leads to a marked improvement in hydroelectrolytic disorders, and sometimes nephrocalcinosis [7]. Under this treatment, after the immediate neonatal period with its complications, the evolution of antenatal Bartter syndrome is generally favourable and is similar to the clinical presentation of classic Bartter syndrome.

The renal prognosis of Bartter syndrome is threatened by episodes of extracellular dehydration [7]. In the long term, the development of proteinuria and chronic kidney disease has been described in patients with Bartter type III [8] or Bartter type IV [7].

9. TREATMENT

Limited clinical evidence regarding treatment exists due to the rarity of the syndrome. Treatment can vary widely among physicians and clinics and is based mainly on the understanding of renal physiology, reported clinical observations, and individual experiences. The classical pharmacological therapy includes potassium chloride supplementation, prostaglandin inhibitor (indomethacin), and aldosterone antagonist (spironolactone). [6].

Sodium supplementation is an integral part of treatment, especially in childhood. It is important to tell patients with these syndromes not to restrict their naturally high sodium intakes. Potassium-rich foods such as fruit juices, nuts, dried fruit or bananas are often offered. These foods can provide a large amount of glucose and calories. [7].

In addition to potassium supplementation, which is often not well tolerated in higher doses, the use of potassium-sparing diuretics, such as spironolactone, eplerenone, or amiloride, should help to raise serum potassium and reverse metabolic alkalosis. Spironolactone and eplerenone block aldosterone receptor but because hypokalemia may induce lower aldosterone levels, some investigators have hypothesized that amiloride (a direct ENaC channel inhibitor) could possibly work better. Besides, gynecomastia, an undesirable effect, which may limit spironolactone use, is not observed with amiloride. [6].

Angiotensin-converting enzyme inhibitors can be used either when proteinuria is present or to help correction of low K⁺ levels [6]. Because polyuria and dehydration are common symptoms, caution is necessary due to the potential risk of acute kidney injury in this high-risk group of patients. Some authors suggest starting therapy using doses below the minimum one and always providing adequate fluid intake. [9]. Angiotensin receptor blockers probably have similar performance, but there are lack of data in this group of patients with BS.[6].

Both indomethacin and selective cyclooxygenase (COX)-2 inhibitors (eg, rofecoxib and celecoxib) relieve symptoms of salt-losing tubulopathy, including hyperprostaglandinuria, secondary hyperaldosteronism, hypochloremic hypokalemic metabolic alkalosis, polyuria, and hypercalciuria. [10] Indomethacin is also associated with

improved growth velocity in BS patients [10]. Our patient was supplemented with potassium and treatment with indomethacin with favorable outcome.

Monitoring of side effects is essential because indomethacin use has been associated with ulcers, necrotizing colitis, and gastrointestinal perforations in preterm infants [10]. Due to significant cardiovascular side effects, rofecoxib is no longer commercially available. It is also unclear whether and at what age COX-2 inhibitors should be discontinued [10].

Growth problems are a common presenting symptom in this population; therefore, when fluid, salt, and nutrition management has been optimized, growth hormone (GH) therapy should be considered. GH deficiency has been reported in concert with both BS and GS [11]. However, even in cases with normal insulin-like growth factor (IGF)-I and GH levels, patients often experience poor growth. Animal models suggest that chronic hypokalemia may inhibit pituitary GH secretion and may also cause tissue-specific alterations in IGF-I and GH metabolism [12]. Patients do respond to GH therapy, although cost of GH treatment is a consideration. [13].

10. PERSPECTIVES

The evolution under a well-conducted treatment is most often benign, with a catching-up of growth; and normal psychomotor development. However, patients with Bartter Syndrome are smaller than the general population, often with delayed puberty. [14].

11. CONCLUSION

Bartter Syndrome is a rare genetic, autosomal recessive, renal tubular disease. The prognosis is dominated, in the short term, by the severity of hypokalemia and dehydration and, in the long term, by the possibility of chronic renal failure which is secondary to nephrocalcinosis. The evolution under a well-conducted treatment is usually benign, with growth catching up and normal psychomotor development. The immediate severity of this disease requires rigorous monitoring of the pregnancy. At birth, a clinical and biological assessment should be carried out to make an early diagnosis in order to allow for the management of the disease.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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