

Antenatal Bartter's syndrome

Síndrome de Bartter antenatal

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■ ABSTRACT

Bartter's syndrome is a rare renal tubular disorder with an autosomal recessive pattern of inheritance and an estimated prevalence of 1 per million people. There are two distinct clinical presentations: antenatal Bartter's syndrome and classical Bartter's syndrome. Antenatal Bartter's syndrome is considered the more severe form having its inception *in utero*. The typical features include early onset of foetal polyuria causing maternal polyhydramnios and preterm delivery, intrauterine growth restriction, postnatal polyuria and dehydration, nephrocalcinosis and osteopenia. We herein report a case of a newborn with antenatal Bartter's syndrome, early suspected due to the familial and antenatal history. A 31 weeks gestation baby was born from consanguineous parents. Pregnancy was complicated with polyhydramnios at 24 weeks of gestation. The newborn developed polyuria, dehydration, electrolyte imbalances and metabolic alkalosis. Additionally, secondary hyperaldosteronism and hyperreninaemia with normal blood pressure were found. His older brother, also born preterm, had nephrocalcinosis and hypercalciuria attributed to prematurity and its complications. A diagnosis of Bartter's syndrome type 2 was made by molecular study, which helped to clarify the clinical picture of his older brother. Antenatal Bartter's syndrome manifestations can be neglected and undercovered by the diagnosis of prematurity. Hence, obstetricians and paediatricians should be aware of this rare disorder. A complete and careful clinical history is of the utmost importance to reach a definitive diagnosis.

Key-Words: Antenatal Bartter's syndrome; electrolyte imbalance; polyhydramnios; polyuria; prematurity.

■ RESUMO

A Síndrome de Bartter é uma doença renal tubular rara, de transmissão hereditária autossómica recessiva, com uma prevalência estimada de 1 por milhão de pessoas. Existem duas formas distintas de apresentação clínica: síndrome de Bartter antenatal e síndrome de Bartter clássica. A síndrome de Bartter antenatal é considerada a forma mais grave, tendo início *in utero*. As características típicas incluem o início precoce de poliúria fetal condicionando polidramnios materno e parto prematuro, restrição de crescimento intrauterino, poliúria e desidratação pós natais, nefrocalcinose e osteopenia. Apresentamos o caso de um recém-nascido com síndrome de Bartter antenatal suspeitado precocemente devido à história familiar e pré-natal. A gravidez foi complicada às 24 semanas por polidramnios. Nasceu um prematuro de 31 semanas, filho de pais consanguíneos. O recém-nascido desenvolveu poliúria, desidratação, distúrbios hidroeletrólíticos e alcalose

metabólica. Adicionalmente apresentava hiperaldosteronismo hiperreninémico, com tensão arterial normal. O irmão mais velho, nascido prematuro, tinha nefrocalcinose e hipercalcúria que foram atribuídas à prematuridade e às suas complicações. Foi feito o diagnóstico molecular de síndrome de Bartter tipo 2, o que ajudou a clarificar o quadro clínico do irmão mais velho. As manifestações da síndrome de Bartter podem ser descuradas e encobertas pelo diagnóstico de prematuridade. Desta forma, obstetras e pediatras devem estar cientes desta doença rara. Uma completa e cuidadosa história clínica é fundamental para chegar ao diagnóstico definitivo.

Palavras-Chave: Distúrbios eletrolíticos; polidrâmnios; poliúria; prematuridade; síndrome de Bartter antenatal

■ INTRODUCTION

Bartter's syndrome is a rare renal tubular disorder with an autosomal recessive pattern of inheritance and an estimated prevalence of 1 per million people¹. The primary pathogenic mechanism is a defective transepithelial chloride reabsorption at the thick ascending limb of loop of Henle. As a result, hypokalemia, metabolic alkalosis and hyperreninaemic hyperaldosteronism occurs with normal blood pressure¹⁻³.

There are two distinct clinical presentations: antenatal Bartter' syndrome (ABS) and classical Bartter' syndrome³. The former, also termed "hyperprostaglandin E syndrome", is the more severe form having its inception *in utero*. The typical features include early onset of fetal polyuria causing maternal polyhydramnios and preterm delivery, intrauterine growth restriction, postnatal polyuria, episodes of dehydration, nephrocalcinosis and osteopenia^{2,3}.

Molecular studies allowed identification of different subtypes of the syndrome, depending on genes involved in defective synthesis of proteins responsible for transport of various ions across tubular cells. Genes reported so far are SLC12A1(15q15-21) encoding the sodium-potassium-chloride co-transporter protein NKCC2 (type1), KCNJ1(11q21-25) encoding renal outer medullary potassium channel ROMK (type2), CICNKB (1p36) which encodes the chloride channel Kb (type3), BSND (1p31) encoding the common accessory B-SUBMIT Barttin for CIC-Ka and CIC-Kb chloride channel (type4) and CASR gene (3q13) encoding the calcium ion-sensitive receptor CaSR (type 5)⁴. Types 1 and 2 are denominated ABS, because of their early clinical presentation. Type 3,

also known as classic Bartter's syndrome is detected during childhood and presents with growth delay, polyuria, polydipsia and anorexia. Type 4 is associated with neurosensorial deafness. Patients with type 5 develop parathormone deficit, as well as the symptoms that are common to all types of the syndrome⁵.

We herein present a case of ABS whose diagnosis was early suspected due to familial and prenatal history.

■ CASE REPORTS

A premature newborn male was born at 31 weeks and 3 days of gestation. He was the second child of consanguineous parents within the third degree, but otherwise healthy.

Pregnancy was complicated by severe polyhydramnios at 24 weeks, which led to hospitalization and therapeutic amniodrainage at 28 weeks of gestation. Biochemical analysis of the amniotic fluid was not performed. Prenatal ultrasounds and foetal echocardiography were unremarkable, as well as maternal serologies and glucose tolerance test. Foetal karyotype was 46, XY normal. Spontaneous delivery occurred at 31 weeks gestation, made through caesarean section because of breech presentation. There was no need for reanimation (Apgar scores 9/7/9) and birth weight was 1830 g (appropriate for gestational age). The newborn was admitted at the intensive care unit because of prematurity.

The newborn had a 5-year-old sibling, born at 29 weeks. That pregnancy was also complicated

Table I

Laboratory Investigation

Investigation	D1	D3	D4	D5	D7	D9	D32
pH	7.3	7.32	7.3	7.33	7.35	7.47	7.5
HCO ₃ ⁻ (mmol/L)	31.3	32.3	31.4	28.3	31.8	30.7	35.4
Serum K ⁺ (mmol/L)	7.6	7.1	7.8	7.4	6.1	4.9	3
Serum Na ⁺ (mmol/L)	128	130	125	122	131	126	134
Serum Cl ⁻ (mmol/L)	94	91	86	87	96	88	89
Serum Mg ³⁺ (mg/dl)	-	3.41	3.83	-	-	-	-
Serum Creatinine (mg/dl)	-	0.77	-	-	-	-	-
Fractional excretion Na+ (%)	-	3.7	-	-	-	-	-
Fractional excretion K+ (%)	-	19.3	-	-	-	-	-
Fractional excretion Cl- (%)	-	4.7	-	-	-	-	-
Urine calcium:creatinine (mg/mg)	-	0.67	-	-	-	-	-
Serum Aldosterone (uU/ml) (normal 7-76)	-	-	-	-	→ 500	-	-
Active serum renin (pg/ml) (normal 40-310)	-	-	-	-	→ 1500	-	-

by polyhydramnios at 25 weeks gestation. He had several complications in the neonatal period (acute renal failure, sepsis, intestinal perforation and resection), with hyponatraemia and hypokalaemia, requiring transient supplements of sodium and potassium chloride, but after this period electrolyte imbalances were not found. Afterwards, he was transferred and followed in a secondary hospital. Later on, short stature, failure to thrive, nephrocalcinosis and hypercalciuria were detected. However, there was no clear diagnosis for those findings.

The newborn's physical examination was normal, without dimorphisms or anomalies of the external genitalia, and he had normal blood pressure. Marked polyuria since the 4th day of life (D₄) was observed, with a maximum urine output of 8 ml/kg/h, and several electrolytic imbalances requiring correction. Maximum weight loss was 18% of the birth weight at D₄ and birth weight was regained at D₂₀. He presented hypochloremia, hyponatraemia, hyperkalemia up to D₇, metabolic alkalosis after the first week of life and hypokalemia since D₃₂ (Table I). The fractional urinary excretion of sodium, potassium and chloride were increased and hyperreninaemic hyperaldosteronism was observed. The renal ultrasound at D₃ was normal and at D₃₆ was suggestive of macroscopic nephrocalcinosis (both renal sinuses had hyper-reflected spots); at 8 months **medullary nephrocalcinosis** was confirmed (the medullary pyramids were hyperechoic, bilaterally, and cortical thickness was preserved with no signs of hydronephrosis).

Molecular diagnosis for Bartter's syndrome was performed, revealing the presence of a mutation c.158T > G (p. Phe53Cys) in homozygosity in the KCNJ1 gene, described as pathogenic for Bartter's syndrome type 2.

The treatment consisted in correction of dehydration and of electrolyte imbalances, with a maximum maintenance fluid of 200 ml/kg/day and of sodium 15 mEq/kg/day. Potassium supplements were introduced at D₃₄. The baby was discharged at D₃₈ with supplements of sodium chloride (10 mEq/kg/day) and potassium chloride (2 mEq/kg/day). On follow up, failure to thrive was observed, with an evolution for height and weight under percentile 3 based on the World Health Organization (WHO) child growth charts. Language delay was also detected, but with no changes regarding hearing acuity.

Currently, he is 21 months old and continues on a potassium supplement, having stopped the sodium supplementation at 4 months old. Until the present, indomethacin has not been introduced and the patient remains free of electrolyte imbalances.

DISCUSSION

The ABS is the severe form of Bartter's syndrome with onset in utero³ and can be suspected and diagnosed before birth. Unexplained polyhydramnios between 24 and 30 weeks of gestation, without apparent foetal or placental abnormalities should

lead to the suspicion of this entity³. Prenatal diagnosis can be made by documenting high chloride content of the amniotic fluid and mutational analysis of genomic DNA extracted from cultured amniocytes obtained by amniocentesis^{4,6}. The mother can be treated antenatally with indomethacin, which improves the prognosis^{3,4}. Indomethacin therapy and therapeutic amniocentesis usually allow the pregnancy to continue³. Unfortunately, in our case, despite having performed amniodrainage, biochemical analysis of the amniotic fluid, which would have led to an early diagnosis, was not made.

In our patient, the diagnosis of ABS was suspected early due to the family history and pregnancy antecedents: parent's consanguinity; two pregnancies complicated by polyhydramnios and an older sibling born prematurely with nephrocalcinosis and hypercalciuria.

Postnatally, patients usually exhibit hyposthenuria and rapid weight loss. Major derangements are severe dehydration, hyponatremia, hypochloremia, hypokalaemia and metabolic alkalosis. Our case report presented all those features. On the other hand, we also observed transient hyperkalemia that may be also occur in type II ABS^{1,3,7}. Despite the hyperkalemia detected during the first week of life, it could have been confused with hypoaldosteronism or pseudohypoaldosteronism type I, the presence of a normal blood pressure was consentaneous with type II ABS. Furthermore, nearly all ABS patients develop medullary nephrocalcinosis within the first month of life¹, which was also observed by us.

Although presumptive diagnosis of ABS can be made on clinical and laboratory grounds, only the molecular study allows a definitive diagnosis and subsequent genetic counseling⁸. In our case, the molecular study confirmed the diagnosis of Bartter's syndrome type 2 and helped to clarify the diagnosis of his elder brother, that albeit having the typical features of this syndrome in the prenatal and neonatal periods, the whole picture was attributed to prematurity and its complications, with impact in his management. Although the molecular study was not performed, he started indomethacin and potassium supplement, improving his appetite and weight.

There is no specific treatment, correction of dehydration and electrolyte imbalance are the important

aspects of management. Generally, the use of prostaglandin synthetase inhibitors is required to control disease, indomethacin being the most recommended and well tolerated in children. Benefit from initiation of indomethacin therapy at 4-6 weeks with low doses (below 1 mg/kg/day) is more likely in patients with mutations at the ROMK channel gene⁷. In our patient, the early suspicion of diagnosis allowed the anticipation and more aggressive correction of dehydration and electrolyte imbalances, being aware that potassium supplements are usually needed by 2-3 weeks of age^{1,7,9}. The newborn was discharged on the 6th week of life, so we decided not to start indomethacin because of the risk of necrotizing enterocolitis and acute renal failure before this age^{1,3,7}.

The long-term prognosis is generally good, but close attention to electrolyte balance, volume status and growth is recommended. However, in a small minority of patients, hyperoxaluria, nephrocalcinosis and chronic indomethacin therapy can lead to chronic interstitial nephritis and chronic renal failure¹⁰.

This disorder is usually severe in the neonatal period and early childhood but it improves gradually which allows to reduce the intensity of treatment or stop it for a period¹. The majority of children with a timely and appropriate therapy have clinical improvement and catch up growth. Long-term outcome including mental development is usually normal³.

■ CONCLUSION

The ABS is a rare entity but it should be suspected in any neonate with antenatal history of unexplained and rapidly increasing polyhydramnios in the late second trimester, that presents during the early neonatal period with polyuria and severe dehydration.

We wanted to leave a word of caution, namely to obstetricians and paediatricians as to the importance of making a complete and careful clinical history, because ABS manifestations can be neglected and mislead by the diagnosis of prematurity.

Early intervention and specific treatment options play a great role in reducing the complication rates of the affected neonates and should be initiated as soon as possible⁷.

Conflict of interest statement: None declared

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