Case report

Recurrent urinary tract infections in an infant with antenatal Bartter syndrome

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Background: **Antenatal variant of Bartter syndrome is characterized by a history of polyhydramnios, premature birth, metabolic alkalosis, hypokalemia, polyuria and renal salt wasting. In this report we present a premature female baby with antenatal Barter syndrome who had three episodes of urinary tract infection (UTI), without evidence for congenital anomaly of the kidneys or urinary tract.**

Methods: **Antenatal Bartter syndrome was diagnosed according to the standard criteria. Ultrasound scan and voiding cystourethrography were performed to exclude congenital anomaly of the kidneys and urinary tract.**

Results: **The baby presented with early hyperkalemia and acidosis. The typical biochemical features of the Bartter syndrome were observed in the second month. Despite appropriate treatment she had persistent hypercalciuria. The clinical course was complicated with recurrent episodes of febrile UTIs. Urinary tract system imaging did not demonstrate congenital anomalies. She finally died of severe dehydration, acidosis and renal failure.**

Conclusion: **Since no congenital anomaly of the kidneys or urinary tract was demonstrated in our patient, we believe that severe, persistent hypercalciuria is the most important risk factor for development of recurrent UTIs.**

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Key words: **acidosis;**
antenatal Bartter syndrome;
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Introduction

Antenatal variant of Bartter syndrome is characterized by a history of polyhydramnion, premature birth, metabolic alkalosis, hypokalemia, polyuria and renal salt wasting. Molecular characterization of the antenatal variant is possible. The disease is caused by a mutation in the gene encoding (i) Na-K-2Cl cotransporter ($NKCC_2$), (ii) the outwardly rectifying potassium channel (ROMK), and (iii) barttin (BSND) which was associated with sensorineural deafness.[1,2]

In this report we present a female baby with antenatal Barter syndrome who manifested hyperkalemia and acidosis in the neonatal period but subsequently, during the second month of life, developed typical biochemical features of the syndrome. She had three episodes of urinary tract infection (UTI), which may be related to her persistent severe hypercalciuria.

Case report

An 1810 g baby was prematurely delivered after the 33rd-34th week gestation by caesarean section. The Apgar score was 4, 6 and 7 at 1, 5 and 10 minutes respectively. The pregnancy was complicated by polyhydramnion. There was no consanguinity between the parents. The two previous pregnancies were also complicated by polyhydramnion; the first one was terminated with abortion and the second one with premature birth and early death.

The early clinical course was complicated by severe hyperbilirubinemia necessitating repeat blood exchanges. Initial laboratory tests revealed hyperkalemia (K^+ 6.9 mmol/L), hyponatremia (Na^+ 125 mmol/L), and metabolic acidosis (pH=7.19, HCO_3^- 12.5 mmol/L, BE -14.5mmol/L). Despite normalization of the serum bilirubin values, acidosis and hyperkalemia persisted. There was marked weight loss from 1810 g to 1300 g due to polyuria, which caused clinical worsening with severe dehydration, tachypnea, tachycardia, and hypotonia. Alkalosis was registered for the first time at the age of thirty days (pH 7.51, HCO_3^- 31.0 mmol/L, BE +8.6 mmol/L). Serum K^+ concentration decreased to 1.8

mmol/L and chloride to 79 mmol/L (lowest value).

Since the baby had prolonged clinical instability with frequent episodes of dehydration and urinary electrolyte losses, indomethacin treatment was started at a low dose (0.1 mg/kg per day) at the age of six weeks. This resulted in marked clinical improvement and decrease of urinary water and electrolyte losses, but there was no effect on calciuria, which was persistently high (urinary calcium to creatinine ratio >3.0; normal <2.2). The clinical course was complicated with three episodes of pyelonephritis (*Escherichia coli* responsible for two episodes and *Pseudomonas aeruginosa* for one episode). The baby was given proper intravenous and oral antibiotics and bacteriuria was cleared in all episodes. She had no central venous lines; peripheral veins were used for parenteral therapy. Imaging of the urinary tract with ultrasound scan and voiding cystourethrography did not reveal evidence for obstructive uropathy or vesicoureteral reflux. On ultrasound scan both kidneys had marked increase of the medullary echogenicity suggesting nephrocalcinosis (Fig.). Despite initial improvement with indomethacine the baby poorly tolerated the drug since the age of 3 months. She had frequent episodes of vomiting and dehydration and at the age of five months died of severe dehydration, acidosis and renal failure.

Discussion

Finer et al[3] described a series of 12 babies with antenatal Bartter syndrome with mutations in the renal potassium channel ROMK. All babies were prematurely born and had postnatal polyuria and dehydration; their potassium was high on the third postnatal day (9.0± 1.2 mmol/L) and normalized by the end of the first week. Peters et al[4] found transient hyperkalemia in 9 of 14 patients with antenatal Bartter syndrome with confirmed ROMK mutations and their phenotype resembled very much to pseudohypoladosteronism type 1. Recently Nozu et al[5] reported a patient who had been misdiagnosed to have pseudohypoldosteronism in the neonatal period; as an adolescent he was found to have normal serum potassium, hypercalciuria and nephrocalcinosis. Mutational analysis of the *KCNJ1* gene revealed novel mutation. Cho and Guay-Woodford[6] also reported a baby who mimicked pesudohypoaldosteronism in the neonatal period; a correct diagnosis was established after detection of mutation in the ROMK.

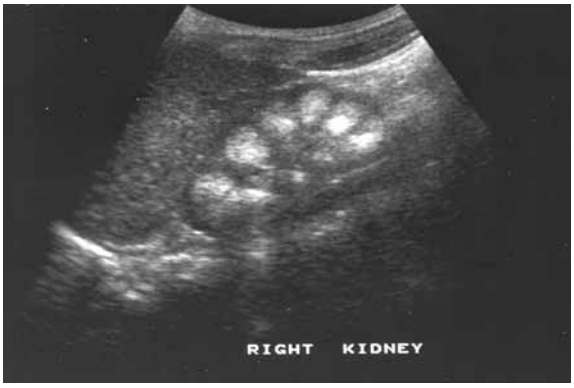

Fig. Ultrasound scan of the right kidney showing medullary nephrocalcinosis.

Similarly to the above-mentioned cases and series, our patient presented with early acidosis and hyperkalemia. The typical biochemical indices, alkalosis and hypokalemia, were evidenced in the second month of life. Clinical and laboratory features showed that our patient represented Bartter syndrome type 2. The genes responsible for antenatal Bartter syndrome were analyzed but mutation was not detected. In the beginning we had some success in controlling water and electrolyte losses with indomethacin. The treatment with indomethacin might be associated with many and severe complications. A new cyclooxygenase-2 inhibitor rofecoxib has been successfully administered to a baby with severe neonatal Bartter syndrome resistant to treatment with indomethacin.[7]

Our patient had recurrent UTI despite absence of structural abnormalities of the urinary tract. The baby had hypercalciuria, which was not controlled by indomethacin. There is no comprehensive evaluation of the prevalence of UTI in children with Bartter syndrome. In their series of 11 children with antenatal Bartter syndrome at present, Shalev et al[8] reported that 3 of them manifested UTI in the neonatal period. There is increasing evidence that hypercalciuria is a risk factor for UTI.[9-12] Idiopathic hypercalciuria UTI was found in 50 (40%) of 124 children.[9] Lopez et al[10] reported that in 164 children with UTI, 32% were found to have idiopathic hypercalciuria. Stojanović et al[11] found in their series of 75 children with UTI, idiopathic hypercalciuria accounted for 21%. In the subgroup of children with recurrent UTI, this percentage increased to 44%.

Weber et al[12] reported the results of a multicentric cooperative study on clinical and genetic aspects of 33 patients with familial hypomagnesemia with hypercalciuria and nephrocalcinosis. At presentation 43% of their patients presented with UTI; during the follow-up period this number increased to 69%. Since hypercalciuria is a classical biochemical feature of Bartter syndrome, one may expect UTI as a logical consequence.

Whatever the etiology of hypercalciuria, it seems

to be a significant risk factor for UTI per se. Lieske et al[13,14] have shown that adherence of calcium oxalate monohydrate crystals on uroepithelial cells may result in their damage and modification of cellular defence mechanisms thereby promoting bacterial invasion.

Besides hypercalciuria, an alternative explanation for UTI might be the higher degree of polyuria in patients with antenatal Bartter syndrome. This might induce a "lazy bladder syndrome" with incomplete voiding. Due to polyuria these patients have frequent episodes of dehydration with subsequent constipation, which is a well-known risk factor for UTI. Also, one may speculate that these babies are at increased risk for development of UTI due to the mild immunosuppressive effect of indomethacin, frequent venous punctures and placement of central venous lines for parenteral hydration.

In conclusion, our patient had recurrent episodes of febrile UTI although imaging studies did not reveal the presence of congenital anomaly of the kidneys or urinary tract. Hypercalciuria is a very important factor for occurrence of UTI in children with Bartter syndrome as it has already been documented in patients with various hypercalciuric diseases. Pooling data are needed from many nephrological centers undertaking a prospective multicentric study to confirm or reject this hypothesis.

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