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CORRESPONDENCE

Antenatal Bartter syndrome resembling nephrogenic diabetes insipidus in a 5-year-old boy

Gwo-Tsann Chuang [a], Shih-Hua Lin [b], Yong-Kwei Tsau [a], I-Jung Tsai [a,*]

[a] *Department of Pediatrics, National Taiwan University Children Hospital, Taipei, Taiwan*
[b] *Division of Nephrology, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan*

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A 5-year-old boy came to our outpatient clinic because of polyuria and polydipsia. His urine output was approximately 3.5 L/d. His laboratory data showed normal serum electrolytes and osmolality. The boy later suffered from vomiting and general weakness. He visited our emergency department and was hospitalized because of severe hypokalemia (1.9 mmol/L). His blood pressure was 105/73 mmHg. The blood gas tests initially showed metabolic alkalosis (pH 7.45, pco_2 40.0 mmHg, HCO_3^- 27.5 mmol/L), where the urine chloride level was 14 mmol/L. The fractional excretion of potassium and sodium was 78.7% and 2.2%, respectively. Hypercalciuria was also noted [urine Ca (mg/dL)/urine Cr (mg/dL) = 1.69]. Furthermore, renal sonography revealed bilateral medullary nephrocalcinosis, hydronephrosis, and hydroureters (Fig. 1). Because Bartter syndrome (BS) was suspected, molecular gene analysis was carried out. Two intronic mutations in the Na^+–K^+–$2Cl^-$ cotransporter gene—one in the consensus splicing site and the other as deep intronic mutation—confirmed the diagnosis of type I BS. In addition, marked polyuria was noted with urine output up to 11 L/d. Urine osmolality was only 64 mOsm/kg H_2O. Water deprivation test and pitressin test confirmed the presence of nephrogenic diabetes insipidus (NDI). The molecular study found no mutations in the *AVPR2* or the *AQP2* gene. Therefore, the final diagnosis was type I BS with secondary NDI. The patient received oral potassium chloride and spironolactone after discharge; follow-up visits showed an acceptable serum potassium level (3.2–3.7 mEq/L) and urine output of approximately 2–3 L/d.

Polyuria has generally been defined as urine output exceeding 2 L/m^2/d in children and 6 mL/kg/h in neonates. It could either be hyposthenuria during diabetes insipidus or isosthenuria in conditions such as BS and solute diuresis. This separates type I BS patients from polyuric patients with NDI, who typically display urine osmolality below 100 mOsm/kg H_2O.

Primary or hereditary NDI refers to mutation(s) in the *AVPR2* gene or the *AQP2* gene. Secondary NDI is attributable to hypercalciuria, hypokalemia, lithium, or the use of certain antibiotics.[1] Hypercalciuria is thought to affect AQP2 expression, probably via the calcium-sensing receptor, which is present in the apical membrane of medullary collecting duct cells and inhibits cyclic adenosine monophosphate formation.[2] In animal models, hypokalemia is associated with decreased expression of AQP2.[3] Thus, a characteristic combination of hypokalemia and hypercalciuria in type I BS could be the cause of secondary NDI.

Type I BS, or antenatal BS, is a rare autosomal recessive disorder characterized by salt wasting from

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* Corresponding author. National Taiwan University Hospital, Number 8, Chung Shan South Road, Taipei 10041, Taiwan.
E-mail address: ijtsai@ntu.edu.tw (I.-J. Tsai).

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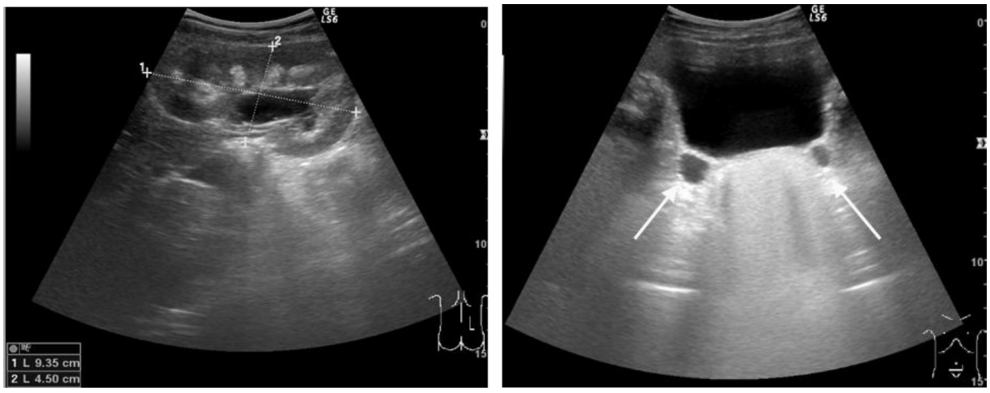

Figure 1 Bilateral medullary nephrocalcinosis, hydronephrosis, and hydroureters on renal ultrasound (white arrows indicate hydroureters).

the thick ascending limb of Henle's loop owing to mutation in the *SCL12A1* gene, which encodes the Na^+—K^+—$2Cl^-$ cotransporter.[4] Patients typically present with maternal polyhydramnios during the fetal period; life-threatening volume depletion, hypokalemia, metabolic alkalosis, along with hypercalciuria and medullary nephrocalcinosis will be noted after birth. Without appropriate treatment, patients with antenatal BS will not survive the early neonatal period. However, late-onset presentation with milder phenotype has been reported with compound heterozygous mutations in the *SLC12A1* gene.[5]

In summary, we delineated a case of antenatal BS presenting coincidentally with NDI beyond the age of infancy. Secondary NDI could be caused by hypercalciuria and hypokalemia. The late-onset phenotype observed in our patient may be explained by a novel compound mutation in the *SLC12A1* gene.

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