Case Report

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Bartter syndrome with long-term follow-up: a case report

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Abstract

Bartter syndrome is a rare inherited disease caused by *CLCNKB* mutation, which results in inactivation of the chloride channel Kb protein. Bartter syndrome is characterized by extreme hypokalemia, hypochloremia, metabolic alkalosis, hyperrenin-induced angiotensinemia, hyperaldosteronemia, and normal blood pressure. We herein report a case of Bartter syndrome that manifested as vomiting, hypokalemia, metabolic alkalosis, normal blood pressure, and significant hyperrenin-induced angiotensinemia. The patient, a 5-month-old girl, carried two known heterozygous pathogenic mutations: c.88C > T (p.Arg30*), which she had inherited from her father, and c.1313G > A (p.Arg438His), which she had inherited from her mother. Treatment with indomethacin, a nonsteroidal anti-inflammatory drug, led to rapid improvement of the hypokalemia, and treatment was continued for 14 years. The indomethacin also induced a sustainable reduction in the hypokalemia and metabolic alkalosis.

Keywords

Hypokalemia, metabolic alkalosis, hyperrenin-induced angiotensinemia, Bartter syndrome, chloride channel Kb, indomethacin

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Introduction

The *CLCNKB* gene encodes chloride channel Kb (ClC-Kb), which is expressed in the thick segment of the ascending branch of the loop of Henle, the distal tubule, and the basolateral membrane of the epithelial cells of the cortical collecting tubules. ClC-Kb plays a very important role in the transmembrane transport of chloride in the renal tubules.[1] Inactivation of ClC-Kb directly leads to reduced chloride reabsorption; the sodium reabsorption associated with chloride will also be reduced, resulting in the loss of water and sodium chloride. This will further activate the renin-angiotensin-aldosterone system and aggravate the loss of potassium. Patients with a mutation in the gene encoding ClC-Kb, a very rare condition, have early-onset hypokalemia due to severe hypokalemia secondary to inactivation of the ClC-Kb protein. Furthermore, the lack of potassium may lead to vomiting and growth retardation. Affected patients also have secondarily increased serum renin and aldosterone levels because of hypovolemia resulting from loss of water and sodium chloride. Therefore, affected patients are prone to hypokalemia and growth retardation during the neonatal period.[2] Type III Bartter syndrome (BS) is caused by mutation of the *CLCNKB* gene.

Symptoms related to the lack of potassium can be fully reversed with nonsteroidal anti-inflammatory drugs (NSAIDs). In contrast, early-onset hypokalemia can only be treated with supplementary potassium, and the success of this treatment is very limited. The patient described in the present report had serious hypokalemia, vomiting and growth retarding before the diagnosis of BS.

It is of great clinical significance to achieve an early diagnosis of BS and adjust the medications in a timely manner according to the changes in the patient's electrolyte levels and growth. We herein present our experience using an NSAID to treat severe hypokalemia in a patient with ClC-Kb protein deficiency.

Case Report

A 5-month-old girl presented with a 3-month history of growth retardation and slightly low muscle tension in the lower limbs. Her mother had a history of hydramnios in the third trimester of pregnancy. The girl's body weight at birth was 3.2 kg, and her development score as a newborn was normal. Physical examination showed that her motor evaluation was equivalent to that of 2- to 3-month-old children, and fine motor and motor growth retardation were observed. Electromyography of the lower limbs showed no abnormalities. Magnetic resonance imaging of the skull showed widening of the left anterior temporal subarachnoid space and bilateral lateral fissure cisterns. She was diagnosed with cerebral palsy. Nutritional nerve therapy and hyperbaric oxygen therapy were given.

The child was readmitted at 10 months of age because of aggravated nausea and vomiting accompanied by malnutrition and mild to moderate dehydration during the rehabilitation training and treatment. Electrolyte measurement revealed a potassium level of 1.24 mmol/L, sodium level of 110.3 mmol/L, chloride level of 60.5 mmol/L, magnesium level of 0.72 mmol/L, and calcium level of 1.17 mmol/L. Blood gas analysis showed a blood pH of 7.602, oxygen partial pressure of 76.3 mmHg, carbon dioxide partial pressure of 37.4 mmHg, bicarbonate of 36.1 mmol/L, and base excess of 13.6. Her serum creatinine level and estimated glomerular filtration rate were normal. The hypokalemia could not be corrected even with venous potassium supplementation at high concentrations. Urine electrolyte measurement showed a urinary potassium level of >20 mmol/L and high urinary calcium level. Her parathyroid hormone level and

blood pressure were normal. Abdominal ultrasound, computed tomography, and renal artery angiography showed no abnormalities. Her renin, angiotensin II, and aldosterone levels were significantly higher than normal (Figure 1(a)). The possibility of BS was considered at this point, and the initial diagnosis of cerebral palsy was suspected to be incorrect.

Next-generation sequencing of the proband (355 genes) showed that the patient carried two known heterozygous pathogenic mutations: c.88C > T (p.Arg30*) and c.1313G > A (p.Arg438His). Thus, she was diagnosed with typical BS (type III), namely that with the *CLCNKB* mutant genotype. Sanger sequencing of the patient's family further showed that the mother carried *CLCNKB* c.1313G > A (p.Arg438His), which was a missense mutation. The patient's father carried *CLCNKB* c.88c > T (p.Arg30*), a nonsense mutation that has been previously reported. The Sanger sequencing diagram is shown in Figure 2 (a), and the family tree is shown in Figure 2(b).

The patient was given oral potassium chloride (4–6 mmol/kg per day), indomethacin enteric-coated tablets (1–2 mg/kg per day), and antiseton (1–3 mg/kg per day) to reduce potassium loss. The electrolyte disturbance was corrected, and the serum potassium concentration was maintained at a slightly lower level than normal accompanied by correction of alkalosis (Figure 1 (b), (c)). The patient maintained normal growth and development after treatment (Figure 1(c)).

Indomethacin was selected for this patient's treatment because it is small enough to be crushed and dissolved in milk for infants to drink. After 10 years of long-term treatment with indomethacin, the child began to show adverse effects including upper abdominal pain with acid regurgitation, nausea, and vomiting. Considering the gastrointestinal adverse effects of indomethacin, we changed the patient's treatment to ibuprofen sustained-release tablets (6–30 mg/kg per day) at 0.3 g twice per day, continuation of potassium chloride sustained-release tablets (5–10 mmol/kg per day) at 3.5 g twice per day, spironolactone (1–3 mg/kg per day) at 60 mg per day, and discontinuation of captopril tablets. We monitored her fasting electrolyte levels, which were maintained at a slightly lower level than normal. At the time of this writing, 4 years had passed since the change in the combined drug treatments, and no obvious gastrointestinal adverse effects had occurred.

The patient's electrolyte disturbances were basically corrected with potassium supplementation combined with a cyclooxygenase inhibitor. Her overall growth and development were maintained within the normal range. At the time of this writing, she was 14 years old, was 155 cm tall, and weighed 48 kg. Treatment of type III BS with indomethacin in this patient increased her body weight to the level of normal development (Figure 1(c)). Consent for publication of this paper was provided by the patient's mother.

Discussion

BS is an autosomal recessive inherited renal tubular disease caused by gene mutations encoding ion channels or transporters. It was first reported by Bartter et al.[3] in 1962. The main pathogenetic mechanism underlying BS is genetic mutation. BS is divided into types I to V BS and Gitelman syndrome.[4–7] Type I BS is caused by mutations in the sodium-potassium-chloride cotransporter (*SLC12A1*), type II BS is caused by mutations in the renal outer medullary potassium channel (*KCNJ1*),[8] type III BS is caused by mutations in ClC-Kb (*CLCNKB*),[9] type IVa BS is caused by mutations in barttin (*BSND*),[10] and type IVb BS is caused by mutations in ClC-Ka

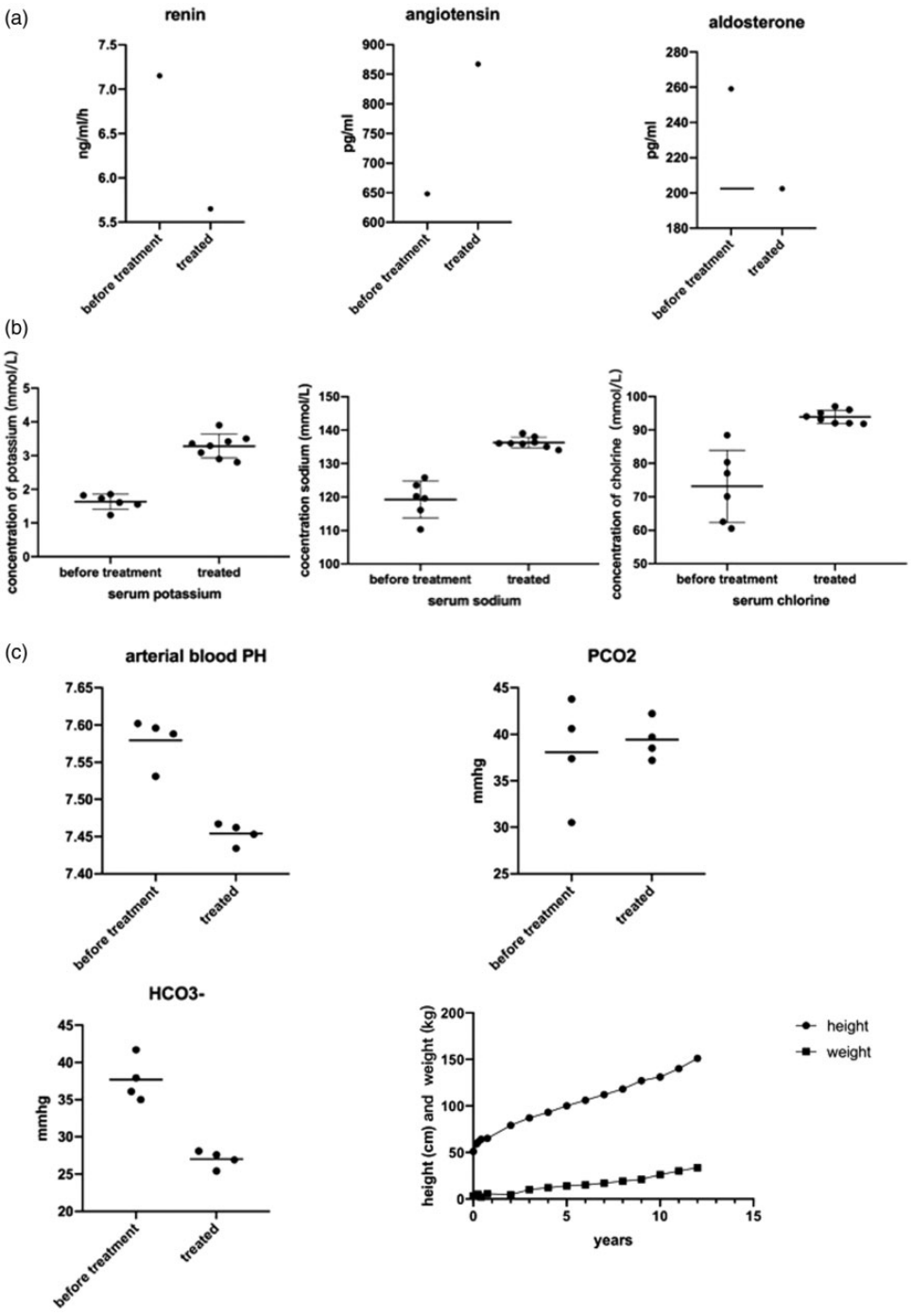

Figure 1. (a) The patient had hyperreninemia, hyperangiotensinemia, and hyperaldosteronemia despite normal blood pressure. (b) The patient had severe hypokalemia, hyponatremia, and hypochlorinemia, but these abnormalities improved after treatment with a non-steroidal anti-inflammatory drug and potassium supplementation. (c) After treatment with indomethacin enteric-coated tablets (1–2 mg/kg per day), the patient's alkalosis was corrected and her height and weight remained close to healthy levels during 14 years of follow-up.

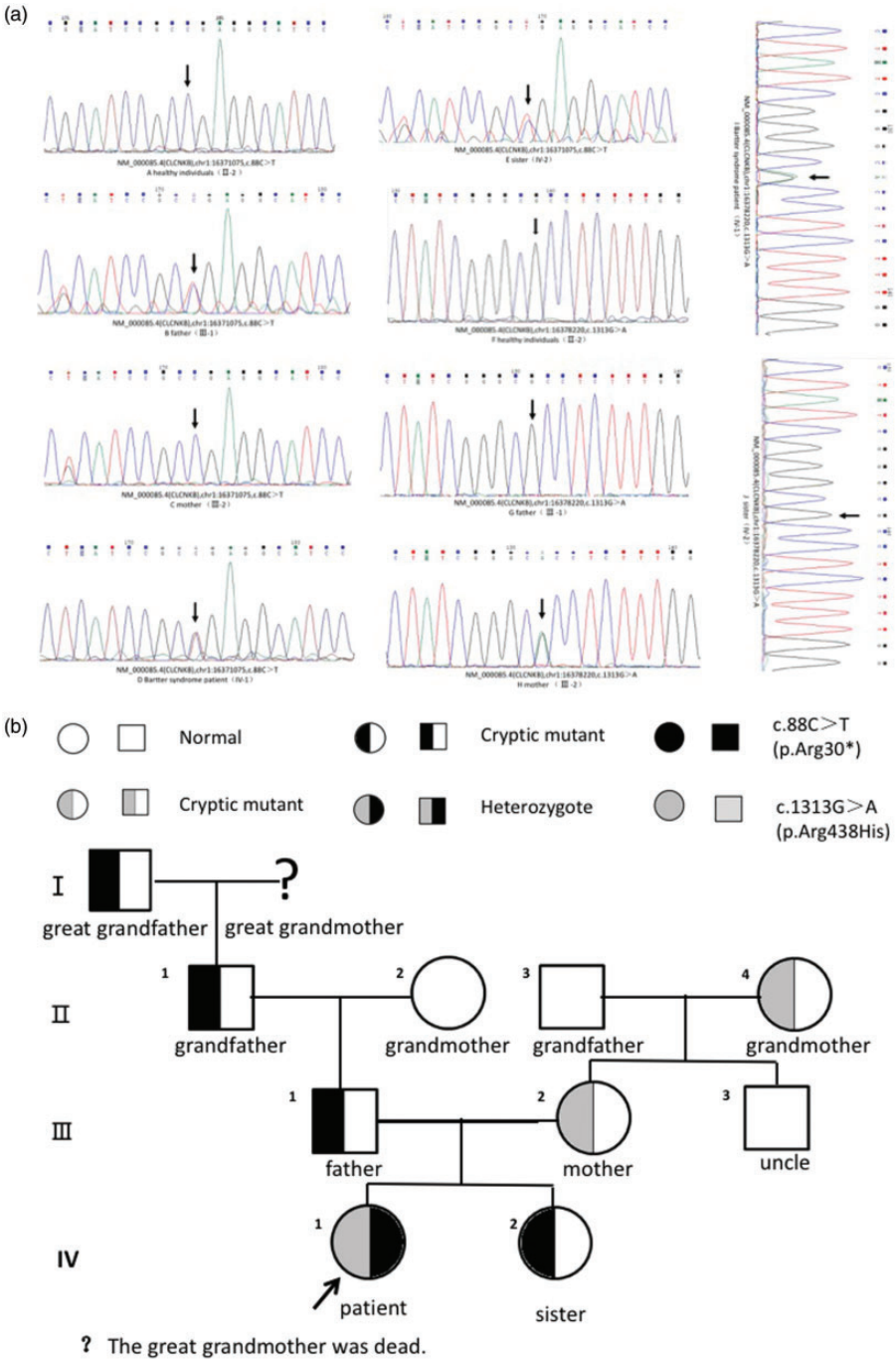

Figure 2. (a) The patient's great-grandfather, grandfather, and father had gene mutations at sites 170 to 180 of *CLCNKB* (c.88C>T). The patient's grandmother and mother had gene mutations at sites 130 to 140 of *CLCNKB* (c.1313G>A). The patient had both of these mutations. (b) The family tree, focusing on the *CLCNKB* gene mutation. The patient had a mutation at sites 170 to 180 of *CLCNKB* (c.88C>T from her father, who had inherited the mutation from his father and grandfather) and another mutation at sites 130 to 140 of *CLCNKB* (c.1313G>A from her mother, who had inherited the mutation from her mother).

and ClC-Kb (*CLCNKA* and *CLCNKB*).[11,12]

The most common clinical type of BS is type III. This type is caused by *CLCNKB* gene mutations in chromosome 1p36, which encodes ClC-Kb, a transmembrane transport protein of chloride in the renal tubules. ClC-Kb is not the only chloride channel in the basolateral membrane of the renal tubules; therefore, type III BS is characterized by less severe electrolyte loss and clinical symptoms than type I and II BS.

BS is more common in infants. Motor retardation and intermittent vomiting were the main manifestations in our patient. Motor retardation should be distinguished from cerebral palsy. The child was given a barium meal, and a computed tomography scan of the digestive tract was performed to eliminate the possibility of pyloric obstruction, intestinal obstruction, and other digestive diseases that children are prone to develop. Intracranial disease, epilepsy, and other central nervous diseases were also excluded. Even if cerebral palsy is suspected because of motor retardation, electrolytes must be measured to differentiate salt-losing tubulopathy.

Hypokalemia is a common clinical outcome of vomiting. However, if it is difficult to correct after potassium supplementation therapy, it should be considered as the initial cause of vomiting. Further examination in the present case showed a significantly high level of urinary potassium, supporting renal potassium loss. If the blood pressure is increased and potassium excretion from the kidney is increased, the primary disease is considered to be caused by excessive mineralocorticoids such as a peribulbar cell tumor, renal artery stenosis leading to primary renal failure, primary aldosteronism, Cushing's syndrome, or Liddle syndrome. In the absence of hypertension and low blood volume, diseases caused by excessive transport of sodium from the distal nephron should be considered, such as diuretic use, BS, or Gitelman syndrome. There has recently been a movement to consolidate BS/Gitelman syndrome into an inherited salt-losing tubulopathy.[13]

It is also important to check for the presence of alkalosis or acidosis according to the blood pH in patients with hypokalemia. In patients with renal potassium loss and metabolic alkalosis, Cushing's syndrome should be identified first; this condition is characterized by hypertension and characteristic signs of hypercorticosis such as central obesity, elevated blood cortisol, and disorder of the circadian rhythm. The presence or absence of primary hyperreninism should also be confirmed. This condition is characterized by severe hypertension and hypokalemia, metabolic alkalosis, and significantly increased renin activity. In addition, the presence or absence of Liddle syndrome should be confirmed. The clinical symptoms of this condition are similar to those of primary aldosteronism and hypertension, but the plasma renin and aldosterone levels are very low. Liddle syndrome is a rare autosomal dominant genetic disease, and spironolactone is ineffective in its treatment.

At present, there is no radical cure for BS, and its treatment is mainly focused on correcting hypokalemia and metabolic alkalosis, supplementing potassium therapy, and reducing potassium loss. The impaired entry of sodium and chloride into the macula densa increases the expression of cyclooxygenase 2; this stimulates renal production of prostaglandin E2, which results in afferent arteriolar dilatation and activation of renin release by the juxtaglomerular apparatus. Therefore, the use of prostaglandin synthesis inhibitors (e.g., NSAIDs), which inhibit the renin-angiotensin-aldosterone system and block prostaglandin synthesis, and potassium retention diuretics may be considered for the management of patients with BS.[14–16] However, careful monitoring is required

because significant adverse effects including renal and gastrointestinal toxicity can occur. After 10 years of indomethacin therapy in the present case, the patient developed abdominal pain, acid regurgitation, nausea, and vomiting. Omeprazole enteric-coated tablets were given. After treatment, the patient's gastric discomfort was significantly relieved. The potassium supplementation was simultaneously adjusted to an indomethacin suppository and potassium chloride solution.

The electrolyte disorders, including the serum potassium, sodium, and chloride abnormalities and metabolic alkalosis, were significantly improved during the treatment of our patient. No significant abnormalities were found in the urea nitrogen level, creatinine level, glomerular filtration rate, urine pH, urine specific gravity, 24-hour urine protein quantification, urine microprotein level, urine β-2 microglobulin level, or urine calcium level. Furthermore, no obvious renal calcification was found. Although drug-induced gastric mucosal injury occurred, the symptoms were significantly relieved after treatment with a gastric mucosal protectant and proton pump inhibitor. Thus, we conclude that even with type III BS, active treatment can improve the patient's height, weight, and biochemical indicators; maintain normal growth and development in children; and provide a comfortable prognosis.

Despite all recent insights, controversy regarding treatment and the lack of experience with long-term follow-up of patients with BS still exist because of the rarity of the disease. Future studies may help to better define the use of NSAIDs in patients with BS.

Author contributions

X.W. performed the scientific literature search, contributed to the data collection and analysis, cowrote and edited the manuscript, and performed the primary figure development. G.Y. performed the scientific literature search, contributed to the data collection and analysis, and cowrote and edited the manuscript. S.C. and M. T. assisted in the literature search and data collection and interpretation and contributed to the figure development. J.L. and S.J. contributed to the data collection and interpretation, figure development, and writing. F.C. and X.W. summarized the patient's history and contributed to the data analysis and interpretation.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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