Review Article

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Bartter Syndrome: Perspectives of a Pediatric Nephrologist

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Bartter syndrome (BS) is one of the most well-known hereditary tubular disorders, characterized by hypokalemic, hypochloremic metabolic alkalosis, and polyuria/ polydipsia. This disease usually presents before or during infancy, and adult nephrologists often inherit the patients from pediatric nephrologists since this is a life-long condition. Here, a few case scenarios will be presented to recount how they first got diagnosed and how their clinical courses were during childhood until adulthood, in addition to a brief review of the disease and its treatment.

Key Words: Bartter syndrome, Hypokalemia, Inherited tubulopathy, Salt-losing tubulopathy

INTRODUCTION

Bartter syndrome (BS) is one of the most well-known hereditary tubular disorders, described initially by Frederic Bartter in 1962[1], characterized by hypokalemic, hypochloremic metabolic alkalosis, and polyuria/polydipsia[2]. This disease usually presents before or during infancy, therefore, patients are rarely diagnosed during adulthood[3]. However, since BS is a life-long condition, they often visit clinics of adult nephrologists. Here, a few case scenarios will be presented to recount how they first got diagnosed and their clinical courses from childhood until adulthood.

Presentation of Bartter syndrome

Clinical vignette #1

A nephrology consultation was sought for evaluation of hypokalemia and alkalosis of a prematurely born 3-day-old boy. He was born after the gestational age (GA) of 32 weeks due to polyhydramnios, which recurred despite repeated amniocentesis. Laboratory tests showed serum Sodium (Na)-potassium (K)-chloride (Cl)-total CO_2 (TCO_2) 133-2.5-84-36 mmol/L, respectively. His birth weight was 1.78 kg (49 percentile) and height was 42 cm (50 percentile), and three days later, his body weight was 1.6 kg despite an intravenous infusion of 325 mL per day (urine output 363 mL per day, 8.5 mL/kg/hr). He did not have other congenital anomalies with a blood pressure (BP) of 79/31 mmHg (95 percentile). Serum blood urea nitrogen (BUN)/creatinine (Cr) levels were 8/0.3 mg/dL, magnesium (Mg) 1.2 mEq/L, renin >83 ng/mL/hr (normal range 11-167 ng/ml/hr in preterm infant[4]), and aldosterone 407 ng/dL (normal range <144 ng/dL[4]). With urinary Na-K-Cl 17-56.1-61 mmol/L and urine calcium (Ca)/Cr 1.43 (mg/mg), his transtubular potassium gradient (TTKG) was 15. Kidney ultrasonography revealed nephrocalcinosis (Fig. 1). Upon clinical diagnosis of antenatal BS from antenatal polyhydramnios, post-natal polyuria (>4 mL/kg/hr), poor oral intake, vomiting, and hypokalemia, a genetic test was done, and the patient was confirmed to be a compound heterozygote of pathogenic variants in *SLC12A1*. After ten days, he was discharged with 7 mEq/kg of potassium chloride (KCl) per day. Indomethacin 1 mg/kg/day was added at six months. He has been admitted to the hospital ten times due to electrolyte imbalance after viral infections. At the last follow-up at age 6, he is doing well with serum Na-K-Cl-TCO_2 139-3.1-

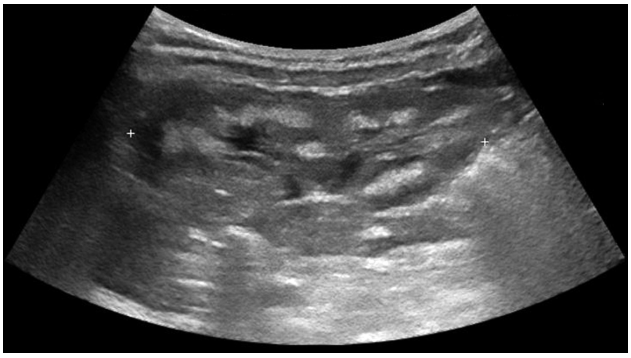

Fig. 1. Nephrocalcinosis.

98-34 mmol/L while taking KCl powder 0.75 g three times a day (1.22 mEq/kg/day) and indomethacin 12.5 mg bid (1.04 mg/kg/day). His BP is 102/68 mmHg (82 percentile). His height is 108.1 cm (3-5 percentile), and his body weight is 16.75 kg (1-3 percentile) despite growth hormone treatment for one year. Nephrocalcinosis persists with urine Ca/Cr 0.94 (mg/mg), and his Cr based estimated glomerular filtration rate (eGFR, using bedside Schwartz equation[5]) is 70 mL/min/1.73 m^2 (serum Cr 0.71 mg/dL).

Traditionally, BS has been classified as antenatal and classical types[6]. Antenatal BS presents before their birth with a history of polyhydramnios and premature delivery[7]. Polyhydramnios is a unique symptom of BS because polyhydramnios of kidney origin occurs only in this condition; not in nephrogenic diabetes insipidus nor congenital nephrotic syndrome, this prenatal symptom accompanies[3]. Since babies with antenatal BS usually are born prematurely, their fluid imbalance and electrolyte abnormalities are noted during their care in a neonatal intensive care unit[8]. Antenatal BS can easily become life-threatening due to severe dehydration[9]. While hypokalemia and metabolic alkalosis are the typical findings of this condition, some antenatal cases may show transient hyperkalemia during the neonatal period if their genetic cause is *KCNJ1* encoding the ATP-sensitive inward rectifier potassium channel 1 (KCNJ1, also known as ROMK), a major channel of potassium secretion in the collecting duct (CD), especially during the neonatal period (BS type 2, BS2)[10]. The other causative channel of antenatal BS, as shown in the vignette, is sodium-potassium-2 chloride cotransporter (NKCC2), the target of the loop diuretics Furosemide encoded by *SLC12A1* (BS type 1, BS1)[11]. Both antenatal BS channels are expressed at the luminal side of the thick ascending limb (TAL) of the loop of Henle (Fig. 2)[12]. Because the paracellular uptake of cations is impaired due to the loss of lumen positivity from defective luminal channels of electrolyte re-uptake, hypercalciuria and nephrocalcinosis are common[3]. Weight gain is often poor for these patients; thus, optimization of calorie intake is sought in addition to water and electrolyte supplementation[13,14]. While nonste- roidal anti-inflammatory drugs (NSAID) are indicated for those who are symptomatic despite ample supplements of electrolytes[15], administration of this medication is often delayed until a few months of age since this class of drugs may cause serious side effects of premature closure of patent ductus arteriosus or necrotizing enterocolitis[16]. Impaired kidney function may happen in BS, especially antenatal BS[17].

Clinical vignette #2

A 5-month-old girl visited a pediatric emergency room for lethargy and vomiting. Previously, her weight gain was insufficient, although she was an avid eater. A few days ago, she caught a common cold and became ill. Her perinatal history was unremarkable, and she was born with a birth weight of 2.8 kg (47 percentile) on GA 37 weeks. Her weight and height were 4.3 kg (0.8 percentile) and 59 cm (35.1 percentile), and her BP was 85/46 mmHg (50 percentile). Laboratory tests showed Na-K-Cl- TCO2 131-2.0-53-52 mmol/L, BUN/Cr 13/0.4 mg/dL, renin >20 ng/mL/hr (normal range 1.4-7.8 ng/ml/hr[4]), aldosterone 40.7 ng/dL (normal range 2-70 ng/dL[4]), serum Ca/phosphorous (P) 12.0/6.6 (mg/mg), Mg 2.3 mg/dL, urinary Na-K-Cl 50-53.1-71 mmol/L (TTKG 17), and urinary Ca/Cr 1.39 (mg/mg). Kidney ultrasonography revealed prominent outer medulla echogenicity throughout both kidneys. Daily oral intake was 100 mL/kg/day, and urine output was 100 mL/kg/day. Genetic tests for classical BS revealed that the patient was a compound heterozygote of pathologic variants of *CLCNKB*. She was managed with intravenous hydration and KCl supplementation. A week later, her condition recovered. Her electrolyte improved to 135-3.3-90 mmol/L with oral supplementation of KCl powder 0.7 g three times a day (27.3 mEq, 6.3 mEq/kg/day), spironolactone 5 mg bid, and celecoxib 5 mg bid (2.3 mg/kg/day). After discharge, she was admitted to the hospital several times dur-

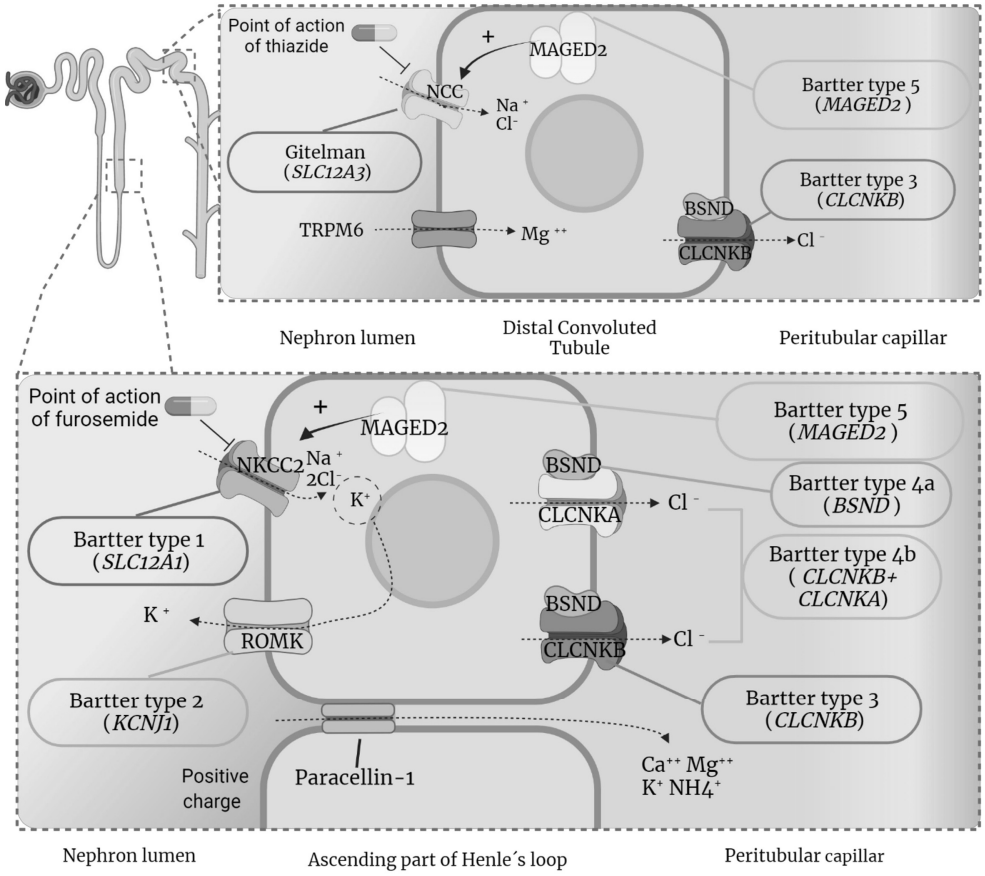

Fig. 2. Channels related to Bartter and Gitelman syndromes. BSND: Barttin; CLCNKA: Chloride channel protein ClC-Ka; CLCNKB: Chloride channel protein ClC-Kb; MAGED2: Melanoma-associated antigen D2; NCC: Solute carrier family 12 member 3; NKCC2: Solute carrier family 12 member 1; TRPM6: Transient receptor potential cation channel subfamily M member 6; and ROMK: ATP-sensitive inward rectifier potassium channel 1[12].

ing acute illnesses such as viral infection by age 6. At the outpatient clinic, her potassium level was between 2.8-3.9 mmol/L, and her magnesium level was between 1.5-2.0 mEq/L. When she was 13 years old, she complained of abdominal pain, and an endoscopic examination revealed a large gastric ulcer. Oral medications were discontinued to heal the lesion, along with the administration of antiacid medications, but it took months to be free of epigastric pain. When her potassium level decreased below 3.0 mmol/L, QT prolongation was noted on electrocardiogram (EKG), and she felt exhausted. She spent 11 months in the hospital at age 15 because of the recurrence of the gastroduodenal lesion. At her age of 16 years, her body weight was 63.7 kg (89.5 percentile), height 150.5 cm (3.6 percentile), body mass index (BMI) 28.1 (99.3 percentile), and BP 109/72 mmHg (50 percentile). Her input and output were up to 6,000-7,000 mL per day.

BS presenting without antenatal symptoms is considered classical BS[6]. Commonly, defects of the basolateral chloride channel CLCNKB manifest as classical BS (BS type 3, BS3). CLCNKB is predominantly expressed in the TAL but the distal convoluted tubule (DCT) and CD as well. Therefore, symptoms of BS3 sometimes overlap with those of Gitelman syndrome; hypomagnesemia may or may not occur, as well as hypercalciuria and nephrocalcinosis[18,19]. Although they are usually diagnosed later than antenatal BS, BS3 is known to be more severe than antenatal BS[3]. They need a massive dose of KCl and NSAID, both ulcerogenic[20]. One would imagine that an enteric-coated formulation might be helpful. But it is dangerous because a large amount of KCl will be relea-

sed simultaneously at a particular intestine site, leading to intestinal mucosa erosion. Enteric-coated KCl supplements were once available but eliminated from the market in the 1970s because they caused perforation of the duodenum and small intestine[21]. Therefore, KCl supplements, preferably slow-release formulations, must be taken after meals (not on an empty stomach). High-potassium food is also recommended; potassium-rich foods include fruits, vegetables, meat, poultry, and fish. One should note that fruits and vegetables contain carbohydrates, which stimulate insulin secretion leading to intracellular translocation of potassium. BS patients often crave salt and salty, processed food; we need to advise the patients to avoid processed food and limit carbohydrates and fat to prevent intake of too much calories not to have high BMI as shown in this vignette.

Cardiac arrhythmia, experienced by this vignette, is a known symptom of hypokalemia. Still, we do not see many cases of arrhythmia in BS cases in the clinic, probably because their hypokalemia is chronic, so their hearts have adapted to hypokalemia, or their arrhythmia is asymptomatic. Nevertheless, arrhythmia may do occur; thus, cardiac evaluations such as stress electrocardiography and Holter monitoring are recommended when indicated[2].

Clinical vignette #3

A seven-year-old boy with BS was found to have hearing loss at a school screening. His BS was clinically diagnosed upon his preterm birth due to polyhydramnios and fluid-electrolyte abnormalities, but a genetic diagnosis was not obtained yet. A hearing test showed that he has bilateral sensory neural hearing loss (bilateral no response to auditory brain stem response, distortion product otoacoustic emission, and transient evoked otoacoustic emissions) requiring cochlear implantation, and genetic test at the hearing clinic revealed that he has a homozygous pathologic variant of *BSND*.

Deafness may accompany BS if both basolateral chloride channels of CLCNKB and CLCNKA are simultaneously defective (BS type 4b, BS4b) or barttin, a subunit required for both basolateral chloride channels of CLCNKA and CLCNKB, is defective (BS type 4a, BS4a). This is because CLCNKB and CLCNKA, along with the barttin subunit, are necessary in the inner ear to depolarize hair cells. Patients may not notice their hearing loss, therefore, screening their hearing, especially for those with BS4s, is mandatory. Hearing is vital to balanced brain development, especially during the early stage of development, and when indicated, a hearing aid can alleviate the impaired auditory center de- velopment. Therefore, genetic diagnosis is better to be obtained, although the genotype-phenotype correlation is yet to be established in BS. BS4s are clinically classified as antenatal BS, and patients may have hypercalciuria, nephrocalcinosis, and hypomagnesemia.

Pathophysiology of Bartter syndrome

Physiologically, almost all the filtered electrolytes to the urinary space are reclaimed while passing through the kidney tubules and collecting duct[22]. In addition, the distal part of DCT and CD secret potassium actively, depending on aldosterone. Sodium reabsorption in the TAL is mainly through NKCC2 of BS1, along with potassium and two chlorides. Then, intracellular chloride is pumped out to the interstitium via basolateral chloride channels CLCNKB of BS3 and probably less significantly by CLCNKA of BS4b, both of which require a subunit barttin of BS4a. Sodium exits from the cell through the universal, basolateral Na-K-ATPase, actively transporting three sodium molecules outward in exchange for two potassium molecules (transport into the cell). Intracellular potassium then returns into the urinary space via the potassium channel KCNJ1/ROMK of BS2, establishing the lumen-positivity. Suppose there are genetic defects or disruption by medication of involved channels or transporters. In that case, electrolytes are not adequately reabsorbed and are lost through urine along with water, thus leading to hypokalemic, hypochloremic metabolic alkalosis resulting in polyuria and polydipsia. Notably, the macula densa of tubuloglomerular feedback (TGF), sensing low tubular chloride concentration, belongs to TAL, and defective channels herein result in the "short-circuiting" of TGF. This leads to uncontrolled activation of cyclooxygenases (especially COX2) producing prostaglandins, stimulating renin hyper-production regardless of volume status[23]. Dr. Bartter himself introduced this syndrome by describing "hyperpla-

sia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis"[1]. In addition to nephrocalcinosis/hypercalciuria from impaired paracellular uptake of cations driven by the transepithelial electrochemical gradient from the lumen-positivity[3], uncontrolled hyper-reninemia from short-circuiting of TGF is a distinguishing feature of BS from Gitelman syndrome, where the salt reabsorption in the DCT is disrupted from defect of *SLC12A3* encoding luminal sodium-chloride cotransporter (NCC).

Diagnosis of Bartter syndrome

Polyuria, hypokalemic, hypochloremic metabolic alkalosis in the context of normal BP despite elevated renin and aldosterone levels are typical symptoms of BS, as shown in the vignettes. In antenatal BS, antenatal polyhydramnios and preterm birth are also typical. However, some BS3 of classical BS presents as antenatal BS or Gitelman-like, probably due to the widespread expression of CLCNKB. Thus, recently BS is classified according to the underlying genetic defects, BS1 to 5 (Table 1), rather than antenatal and classical BS[12,24]. BS5, not described in the vignettes, is caused by mutations in *MAGED2* encoding the protein melanoma-associated antigen D2, affecting the expression of NKCC2 in the TAL and NCC in the DCT[25]. BS5 is a transient but severe antenatal form of X-linked BS, and to the authors' best knowledge, Korean cases of BS5 have not been reported yet. In the past, activating mutations of basolateral calcium-sensing receptor (CaSR) were referred to as BS5 because it may show hypokalemic, hypochloremic metabolic alkalosis, but now it is considered as Bartter-like subform of autosomal dominant hypocalcemia. Some conditions resemble BS, requiring differential diagnosis (Table 2)[26]. Differential diagnosis includes congenital chloride diarrhea, hyperaldosteronism, Gitelman syndrome, and diuretics or laxative abuse (Table 3)[2]. While clinical symptoms and signs are often evident to obtain a clinical diagnosis of BS, genetic confirmation is recommended to provide a definitive diagnosis, prognosis prediction, opportunity for early screening and intervention of hearing impairment, and genetic counseling. Since multiple genes may cause BS and conditions to be differentiated from BS, targeted exome sequencing or whole exome sequencing is recommended (Table 3). Fractional excretion of Cl (>0.5%) or urine Na/Cl >1.6 (mmol/mmol) is typical of BS. Notably, tubular function test using loop diuretics or thiazide is no longer standard care because of the risk of severe dehydration, especially because the efficacy of genetic tests surpasses that of diuretics challenge[2].

Treatment and monitoring of Bartter syndrome

The mainstay treatment of BS is fluid repletion, along with electrolytes and NSAID to inhibit prostaglandin E2. For infants and children, adequate caloric intake is also important along with growth hormone supplementation if necessary, while excessive caloric intake needs to be avoided. Recommended medications and dosages are listed in Table

Table 1. Types of Bartter syndrome according to genes[12]

Bartter subtype	OMIM	Inheritance	Causative gene	Related Protein	UniPort Code
Type 1	601678	AR	*SLC12A1*	NKCC2 (Solute carrier family 12 member 1)	Q13621
Type 2	600359	AR	*KCNJ1*	ROMK (ATP-sensitive inward rectifier K channel 1)	P48048
Type 3	607364	AR	*CLCNKB*	CLCNKB (Cl channel protein CIC-Kb)	P51801
Type 4a	602522	AR	*BSND*	BSND (Barttin)	Q8WZ55
Type 4b	613090	AR	*CLCNKB* + *CLCNKA*	CLCNKB (Cl channel CIC-Kb) + CLCNKA (Cl channel CIC-Ka)	P51801 + P51800
Type 5	300470	XLR	*MAGED2*	MAGED2 (Melanoma-associated antigen D2)	Q9UNF1

AR: autosomal recessive, XLR: X-linked recessive

Table 2. Differential diagnosis of Bartter syndrome[2)]

Leading symptom	Differential diagnosis	Additional findings
Polyhydramnios of fetal origin	Aneuploidy	Abnormal karyotype
	Gastrointestinal tract malformation	Variable, empty stomach
	Congenital chloride diarrhea	Dilated intestinal loops
Salt loss	Pseudohypoaldosteronism type I	Metabolic acidosis, hyperkalemia
Salt loss with Hypokalemic alkalosis	Congenital chloride diarrhea	Low urinary chloride
	Pseudo-Bartter syndrome, e.g., in cystic fibrosis	Low urinary chloride
	Gitelman syndrome	Hypocalciuria, Hypomagnesemia
	HNF1B nephropathy	Renal malformation, cysts, MODY5, hypomagnesemia
	HELIX syndrome	Hypercalcemia, hypohidrosis, ichthyosis
	Autosomal dominant hypocalcemia	Hypocalcemia, seizures
	EAST/SeSAME syndrome	Ataxia, seizures, deafness, developmental delay
	Surreptitious vomiting	Low urinary chloride
	Surreptitious laxative use	Low urinary chloride
	Surreptitious diuretic use	Highly variable urinary chloride
Hypokalemic alkalosis Without salt loss	Primary hyperaldosteronism	Hypertension, low renin
	Apparent mineralocorticoid excess	Hypertension, low renin/aldosterone
	Liddle syndrome	Hypertension, low renin/aldosterone
Nephrocalcinosis	Distal renal tubular acidosis	Metabolic acidosis
	Proximal tubular defects	No metabolic alkalosis
	Familial hypomagnesemia/hypercalciuria	No hypokalemic metabolic alkalosis, Chronic kidney disease
	Apparent mineralocorticoid excess	Hypertension, low renin/aldosterone

HELIX syndrome: Hypohidrosis, Electrolyte imbalance, Lacrimal gland dysfunction, Ichthyosis, and Xerostomia syndrome
EAST/SeSAME syndrome: EAST (Epilepsy, Ataxia, Sensorineural deafness, Tubulopathy) or SeSAME (Seizures, Sensorineural deafness, Ataxia, Mental retardation, and Electrolyte imbalance) syndrome
MODY5: maturity onset diabetes of the young type 5

Table 3. Genes recommended to be included in genetic testing for Bartter syndrome[2)]

Gene	Associated disorder (OMIM)
SLC12A1	BS1 (601678)
KCNJ1	BS2 (241200)
CLCNKB	BS3 (607364)
	BS4b (613090)
CLCNKA	BS4b (613090)
BSND	BS4a (602522)
MAGED2	BS5 (300971)
SLC12A3	Gitelman (263800)
CASR	ADH (601198)
KCNJ10	EAST/SeSAME (612780)
SLC26A3	CCD (214700)
CLDN10	HELIX (617671)
SCNN1A	PHA1B (264350)
SCNN1B	Liddle syndrome (177200)
SCNN1G	
NR3C2	PHA1A (177735)
HSD11B2	AME (218030)
CYP11B1	HALD1 (103900)
CLCN2	HALD2 (605635)
KCNJ5	HALD3 (600734)
CACNA1H	HALD4 (607904)

ADH, autosomal dominant hypocalcemia; AME, apparent mineralocorticoid excess; BS, Bartter syndrome; CCD, congenital chloride diarrhea; EAST, epilepsy, ataxia, sensorineural deafness, tubulopathy; HALD, familial hyperaldosteronism; HELIX, hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, xerostomia; MIM, Mendelian Inheritance in Man

Table 4. Currently used pharmacological treatments for Bartter syndrome

Therapeutic Approaches	Bartter Syndrome
NaCl	≥5–10 mmol/kg/d, slow-releasing tablet 2.4-4.8 g/day #4
KCl	1–2 mmol/kg or higher as slow-releasing or liquid, divided targeting 3.0 mml/L
Mg, when necessary (organic acid)	5 mg/kg (0.2 mmol/kg), slow-release tablets #3-4, with meal
NSAIDs	Indomethacin 1-4 mg/kg/day #3-4 Ibuprofen 15-30 mg/kg #3 Celecoxib 2-10 mg/g/day #2
Gastric acid inhibitors	
Growth Hormone, when indicated	Possible, poor evidence of efficacy

3. Side effects of the medicines warrant caution. Although potassium-sparing diuretics and renin-angiotensin-aldosterone system inhibitors have been considered, this may lead to more volume depletion. Therefore, using those medications is not recommended[2)]. Patients need to avoid proton pump inhibitors (PPI, inhibit magnesium uptake), food containing glycyrrhizinic acid (e.g., licorice root) or exce-

ssive alcoholic beverages (aggravate potassium loss), fruit juice or bicarbonate-rich drink (worsen metabolic alkalosis)[13]. It is recommended to follow the patients every 3-6 months during infancy and childhood and every 6-12 months during adult- hood. In addition to fluid status, electrolytes, and kidney function, pediatricians must monitor growth and development. Kidney ultrasound needs to be performed regularly every 12-24 months to monitor urinary stones or nephrocalci- nosis. Cardiac evaluation is indicated when the patients complain of palpitations or syncope.

Long-term outcomes

For long-term follow-up of BS, chronic kidney disease (CKD) and growth problems are major concerns. Growth of BS is often poor, possibly because of acid-base or electrolyte disturbances in BS or growth hormone deficiency[17,27-30]. Even when growth hormone therapy is indicated, appropriate inhibition of prostaglandin activation needs to be accomplished first. Regarding kidney outcome, proteinuria has been reported in patients with BS as well as CKD. Their pathologic findings of the kidney include "diffuse glomerular and tubule-interstitial lesions with enlarged glomeruli and focal segmental glomerulosclerosis"[17,18,27,31]. CKD may develop later in the course of BS, particularly types 1, 4a, and 4b[17,18,32], and its proposed underlying mechanisms are chronic stimulation of the renin-angiotensin system, periodic dehydration, prematurity, nephrocalcinosis, long-term NSAID treatment, and chronic hypokalemia[33]. However, NSAID use as a CKD risk factor is not yet fully confirmed[34].

CONCLUSIONS

BS is very rare, even for pediatricians. Once coming across a BS case, the physiology and pathophysiology of tubular salt handling are reminded and utilized to manage the patient. Understanding that these patients have undergone multiple near-life-threatening episodes of dehydration and electrolyte abnormalities and have lived on medication for their whole lives would help physicians manage these patients better.

Acknowledgments

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