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Differential diagnosis of perinatal Bartter, Bartter and Gitelman syndromes

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ABSTRACT

The common finding of hypokalemic alkalosis in several unrelated disorders may confound the early diagnosis of salt-losing tubulopathy (SLT). Antenatal Bartter syndrome (BS) must be considered in idiopathic early-onset polyhydramnios. Fetal megabladder in BS may allow its distinction from third-trimester polyhydramnios that occurs in congenital chloride diarrhea (CCD). Fetal megacolon occurs in CCD while fecal chloride >90 mEq/L in infants is diagnostic. Failure-to-thrive, polydipsia and polyuria in early childhood are the hallmarks of classic BS. Unlike BS, there is low urinary chloride in hypokalemic alkalosis of intractable emesis and cystic fibrosis. Rarely, renal salt wasting may result from cystinosis, Dent disease, disorders of paracellular claudin-10b and Kir4.1 potassium-channel deficiency. Acquired BS may result from calcimimetic up-regulation of a calcium-sensing receptor or autoantibody inactivation of sodium chloride co-transporters in Sjögren syndrome. A relatively common event of heterozygous gene mutations for Gitelman syndrome increases the likelihood of its random occurrence in certain diseases of adult onset. Finally, diuretic abuse is the most common differential diagnosis of SLT. Unlike the persistent elevation in BS, urinary chloride concentration losses waxes and wanes on day-to-day assessment in patients with diuretic misuse.

Keywords: acquired Bartter, antenatal Bartter, Gitelman, hypochloremic metabolic alkalosis, pseudo-Bartter syndromes

INTRODUCTION

Bartter syndrome (BS) is a rare autosomal recessive (AR) disorder comprising a defect in the thick ascending limb of the loop of Henle (TALH). Its characteristic findings are hypokalemia, metabolic alkalosis, hyperreninemia and hyperplasia of the juxtaglomerular apparatus [1]. Despite urinary salt wasting, secondary hyperaldosteronism results in the maintenance of euvolemia. Its perinatal presentation may include elevated urinary levels of prostaglandin (PG) E2 [2]. A closely related disorder, Gitelman syndrome (GS), is distinguished by a later age of onset, milder clinical manifestations and a lower fatality rate [3–5]. Despite the increased availability of genetic testing, the diagnosis of BS or GS is largely dependent on clinical features, especially in developing countries. Due to the common findings of hypokalemic alkalosis in more prevalent disorders (e.g. emesis), clinicians must be aware of pitfalls that may confound an accurate diagnosis. Whereas severe perinatal BS may be readily diagnosed, childhood and adult forms of the disease are usually more insidious in presentation [3–5]. In the absence of decompensation from a comorbid illness, late-onset disease often maintains near-normal homeostasis by an adaptive increase in oral fluid and salt intake. Accordingly, the objective of this

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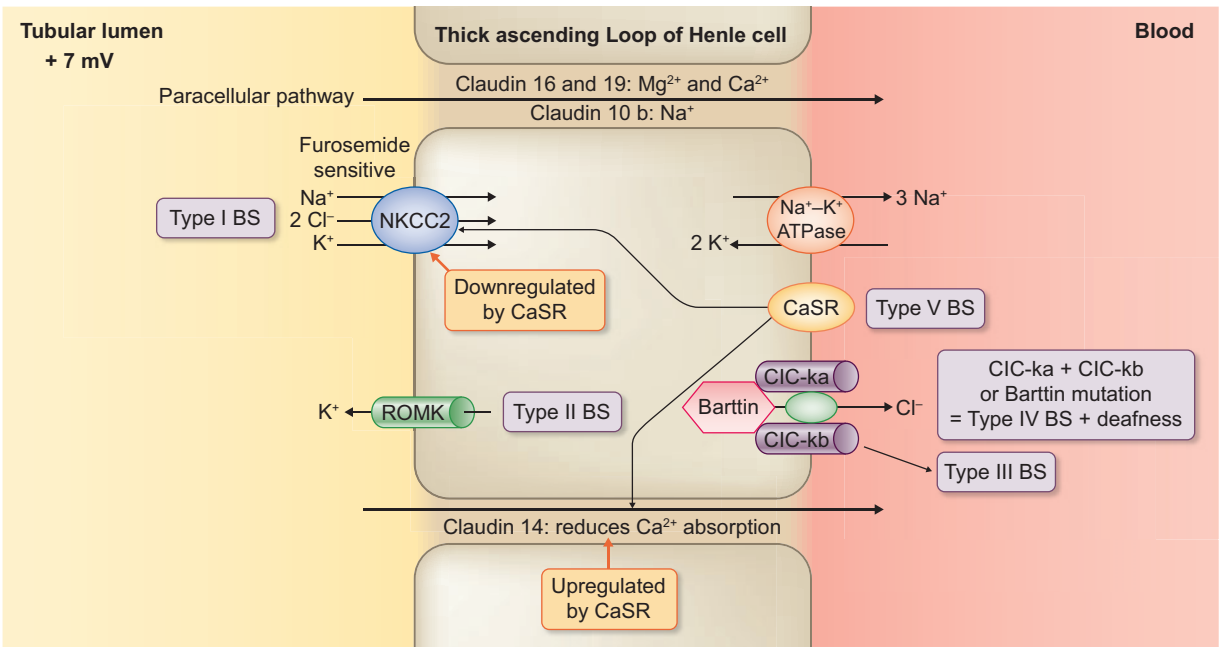

FIGURE 1: Deficits in Electrolyte Transport from the Renal Tubular Lumen across the Thick Ascending Limb of the Loop of Henle Cell Accounting for Types I, II, III, IV and V Bartter Syndrome.

review is to update our knowledge on the salt-losing tubulopathies (SLTs) while highlighting the pathophysiological bases of the major clinical entities that are mistaken for BS or GS.

METHOD

We reviewed relevant literature by conducting a PubMed search using the terms hypokalemic alkalosis, antenatal BS, BS, pseudo-BS, acquired BS, GS and SLT. We retrieved clinical case series, original articles and review article formats. We selected only articles that were published in the English language.

PREVIEW OF HYPOCHLOREMIC METABOLIC ALKALOSIS

Metabolic alkalosis is characterized by a retention of plasma bicarbonate (HCO_3^- >26 mmol/L) that is typically associated with an elevated arterial blood pH >7.45 (alkalemia). It may be initiated either by excessive renal (e.g. use of loop diuretics) or extrarenal loss (e.g. vomiting) of hydrogen ions (H^+) [6]. Alkalosis may also result from the extracellular displacement of H^+ into the cellular space in response to hypokalemia. Sustaining metabolic alkalosis requires an impaired renal capacity to excrete the bicarbonate load [6]. With the resultant low sodium delivery in the distal convoluted tubule (DCT), there is an increase in the activity of the epithelial sodium channel (ENaC), which in turn causes luminal reabsorption of sodium (Na^+) in exchange for H^+ and potassium ions (K^+) [7]. In contrast to the euvolemia in BS and GS, metabolic alkalosis in conditions mimicking primary aldosterone excess, including Liddle syndrome, licorice ingestion and apparent mineralocorticoid excess, is associated with excessive fluid retention and hypertension [8–13]. Furthermore, the two groups of disorders are differentiated by a secondary elevation of serum aldosterone in BS and GS while there is a suppression of the hormone in the latter [9, 10]. Liddle syndrome is caused by a gain-in-function mutation of ENaC, and licorice contains glycyrrhizinic acid, which is a potent substance that inhibits an enzyme that inactivates cortisol, 11-β-hydroxysteroid dehydrogenase type 2 (HSD11B2) [11, 12]. On the other hand, a syndrome of apparent mineralocorticoid excess results from recessive loss-of-function mutations in the gene for HSD11B2 [9, 13].

RENAL TUBULAR PHYSIOLOGY

TALH

Activity of the apical sodium–potassium dichloride (Na^+K^+-$2Cl^-$) co-transporter (NKCC2) results in a 25–30% reabsorption of filtered sodium chloride (NaCl) by the TALH (Figure 1) [14]. Poor water permeability of the TALH, due to the absence of aquaporin expression, produces an optimally diluted luminal fluid while generating a medullary osmotic gradient. The recycling of luminal K^+ generates a positive luminal potential difference (PD), required for the maintenance of NKCC2 activity [15, 16]. Of the two apical K^+ channels, the renal outer medullary K^+ channel (ROMK) Kir1.1 mediates 75% of the basal amount of the K^+ recycling (Figure 1) [17–19]. The cystic fibrosis (CF) transmembrane regulator protein (CFTR) regulates the ROMK channel [20, 21]. In addition, basolateral Na^+/K^+-ATPase activity generates the sodium gradient that facilitates the function of the apical NKCC2 [22]. Furthermore, generation of an intracellular negative voltage (−40 to −70 mV) promotes the extrusion of Cl^- via the basolateral CLC-Ka and -b channels (Figures 1–3) [22–24]. Barttin, an accessory protein, enhances the function of both channels [24]. Apart from the co-expression with CLC-Kb on TALH and DCT, there is also CLC-Ka on the thin ascending limb

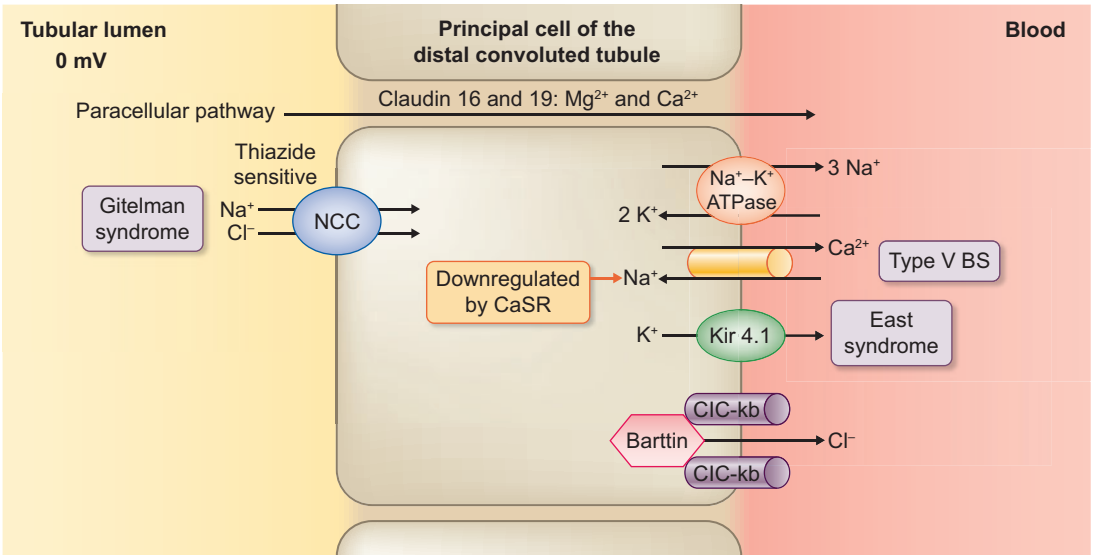

FIGURE 2: Deficits in Electrolyte Transport from the Renal Tubular Lumen across the Principal Cell of the Early Distal Convoluted Tubule accounting for Gitelman Syndrome and EAST/ SeSAME Syndrome.

[25]. The basolateral K^+Cl^- cotransporter KCC4 participates in mediating Cl^- exit into the blood [26]. The positive luminal PD and preferential permeability of cations over Cl^- (aided by claudin-16 and -19) are associated with a net paracellular absorption of Ca^{2+} and Mg^{2+} [27–30]. Similarly, claudin-10b exclusively promotes Na^+ reabsorption across the paracellular pathway [31]. In contrast, paracellular expression of claudin-14, which is upregulated by the basolateral calcium-sensing receptor (CaSR), produces urinary Ca^{2+} excretion [30, 32].

DCT

The DCT reabsorbs 6–10% of the sodium content of glomerular filtrate, principally by means of the NaCl cotransporter (NCCT) (Figure 2) [15, 33]. In addition to the NCCT, the expression of an aldosterone-sensitive ENaC on the late DCT causes a progressive change of the lumen PD from 0 to −30 mV [7, 34]. Apart from the generation of a transepithelial voltage of −60 to −90 mV, the basolateral Na^+/K^+-ATPase pump provides a driving force for the NCCT [35]. In turn, basolateral recycling of the intracellular K^+ via the Kir4.1 channel maintains the activity of the Na^+/K^+-ATPase pump (Figure 2) [36]. Similar to the TALH, a basolateral chloride efflux occurs through CIC-Kb and KCC4 [37, 38]. In addition, the generation of lumen-negative PD by ENaC stimulates the basal amount of K^+ recycling through ROMK [35, 39]. With larger tubular fluid flow and a greater demand for K^+ secretion, there is an activation of (a large-capacitance) maxi-K^+ channel (Figure 3) [18, 19, 40, 41]. Furthermore, active transcellular absorption of both Ca^{2+} and Mg^{2+} occurs via transient receptor potential (TRP) channel subfamily V member 5 (TRPV5) and TRP channel subfamily M member 6 (TRPM6), respectively (Figure 3) [42–45]. Finally, types A and B intercalated cells (ICs) are unique cell types that are expressed in DCT and cortical collecting ducts (CCDs) (Figure 3) [46]. Type A ICs have H^+-ATPase and H^+/K^+-ATPase on the apical membrane for the control of metabolic acidosis [46, 47]. A basolateral Cl^-/HCO_3^- (AE1) exchanger expels the base generated from the luminal H^+ secretion into the blood [46]. In contrast, Type B ICs have the Cl^-/HCO_3^- exchanger (Pendrin) on the apical membrane, which is activated by metabolic alkalosis [46].

PATHOGENESIS AND GENO-PHENOTYPE CORRELATION IN BS AND GS

BS results from several genetic mutations that produce molecular defects in the electrolyte transporters of the TALH and DCT, while inactivation of the thiazide-sensitive NCCT in the DCT causes GS (Table 1, Figures 1 and 2) [1, 2, 4, 5]. To facilitate easier understanding, previous authors have suggested the use of nomenclature that is based on the pharmacological mechanism of equivalent diuretic agents [4, 5].

Perinatal BS and BS

Although genotype–phenotype correlations are variable in BS, five clinical categories are typically recognized [4].

BS Types I and II

Due to the crucial role of NKCC2 on the apical membrane of TALH (reabsorbs 25% of the filtered NaCl), mutation of SLC12A1 produces type I BS [4, 5, 33, 48]. Required to sustain NKCC2 activity, deficiency of potassium recycling by apical ROMK (KCNJ1 mutation) produces Type II BS (Table 1 and Figure 1) [49]. Consequently, both type I and II produce the most severe manifestations. These may be present initially in the second trimester of pregnancy as polyhydramnios, which may result in premature delivery [1, 2, 50, 51]. Furthermore, defective solute transport across the apical membrane of the macula densa may exacerbate tubular salt wasting both in the fetus and in the newborn [52, 53]. A chloride-defective macula densa produces PGE2, which in turn interacts with the EP4 receptor to release renin from the juxtaglomerular granular cell [54]. The release of angiotensin II produces efferent vasoconstriction, as opposed to nitric oxide–mediated afferent vasodilatation [55]. The resultant increase in glomerular filtration rate (GFR) reduces the fractional sodium reabsorption by the proximal tubule (PT). The subsequent increase in distal sodium delivery, in turn, promotes a secondary aldosteronism [7, 8]. In addition to higher GFR, polyuria results from disruption of the medullary osmotic gradient. Extreme free water loss could lead to an erroneous

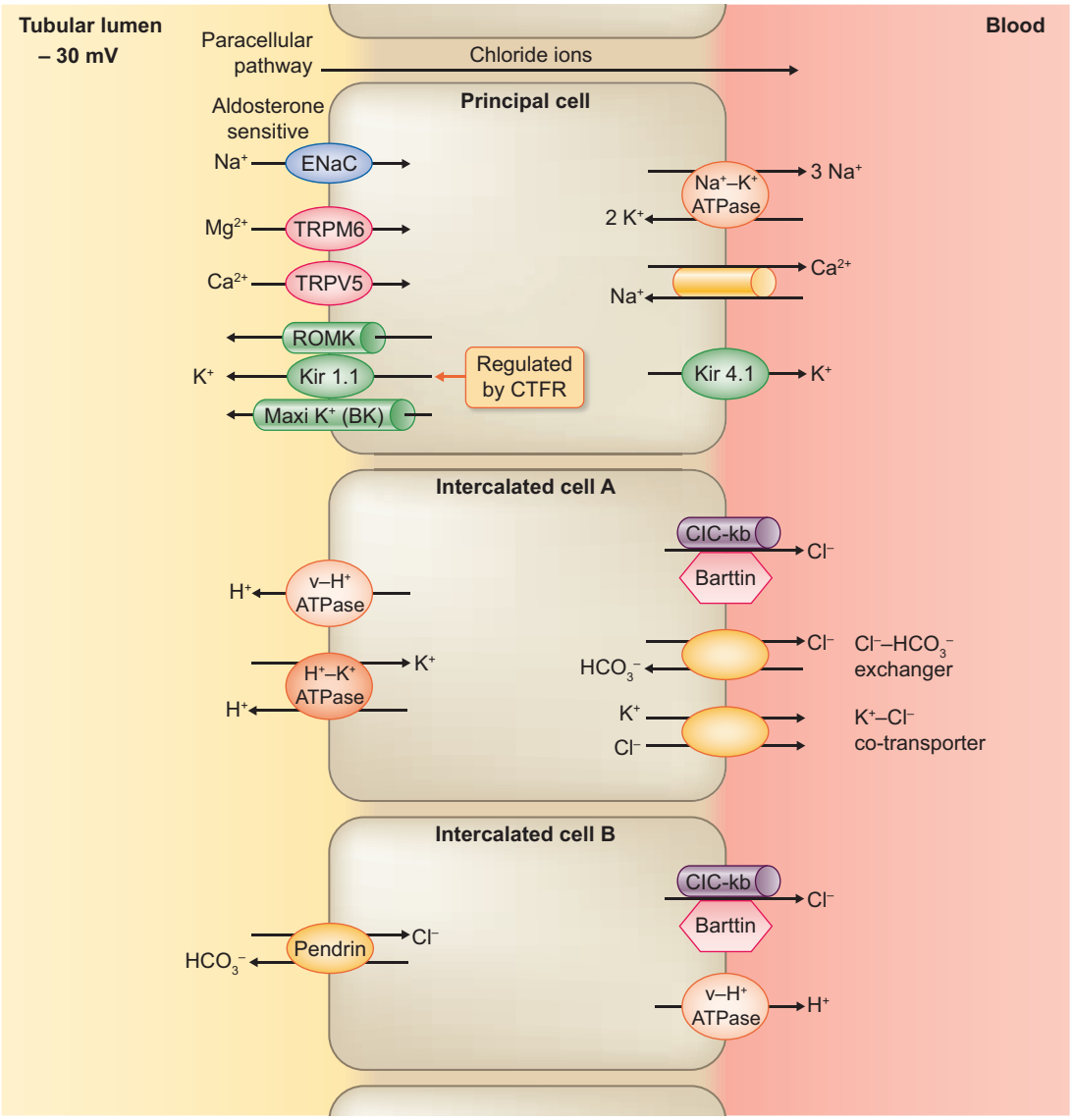

FIGURE 3: Pattern of Electrolyte Transport Across the Principal Cell, Intercalated Type A Cell and Intercalated Type B Cell of the Late Distal Tubule/ Cortical Collecting Ducts.

diagnosis of nephrogenic diabetes insipidus [56]. Impaired NKCC2 reduces the lumen-positive PD that is necessary for paracellular transport of Mg^{2+} and Ca^{2+} [27–29, 57]. Hence early-onset severe hypercalciuria may produce medullary nephrocalcinosis [2, 58]. Newborns with type II BS initially present with hyperkalemia due to inhibition of potassium excretion into the lumen of the late DCT [35, 39–41, 58]. As a result of a developmental delay, the compensatory potassium secretion by the luminal maxi K^+ channel is absent [59, 60]. Named after the pharmacological target of NKCC2, type I BS is also called a furosemide-type loop disorder. Similarly, type II BS has been designated a furosemide/amiloride phenotype because of the roles of ROMK channels in both TALH and late DCT, coupled with ENaC [4, 5, 61].

BS type III, also called the classical variant, is the most common BS phenotype [4, 5]. It is caused by mutations in the *CLCNKB* gene, which encodes basolateral chloride channel variant b (ClC-kb) (Table 1 and Figures 1–3) [62]. The expression of CIC-kb in both TALH and DCT provides the basis for identifying type III BS as a mixed thiazide–furosemide phenotype [4, 5, 63]. Whereas mutation of CIC-kb in TALH is physiologically compensated by the parallel activity of CIC-ka in the thin ascending limb (which exists only in juxtamedullary nephrons, and it represents 15% of the total nephrons in humans), such is not the case with the loss of ClC-kb in the early DCT [25, 64]. For this reason, the observed variable clinical manifestation of BS is more frequently close to the symptom pattern of GS rather than BS. Thus in a study of a cohort of 115 patients with type III BS, 44.5% presented in childhood as classical variant while 29.5% (with a severe gene mutation) had perinatal BS and 26% of cases were indistinguishable from GS [65, 66]. Compared with types I and II BS, antenatal presentation is less severe and nephrocalcinosis is typically absent in infancy [4, 26, 64].

BS type IV is due to either a double heterozygote mutation of genes that encode basolateral CICs (CLC-NKA and CLC-NKB) or a monogenic mutation of the gene that produces their regulatory protein, Barttin [67, 68]. The absence of CICs on both the TALH and DCT segments accounts for a severe perinatal

Table 1. Clinical, genetic and biochemical features of BS and GS

Syndromic type	BS I	BS II	BS III	BS IV a	BS IV b	BS V(ADH)	BS V(MAGE)	GS
Gene mutation	SLC12A1	KCNJ1	CLCNKB	BSND	CLCNKA + B	CASR	MAGED2	SLC12A3
Gene product	NKCC2	ROMK	CIC-kb	Barttin	CIC-ka + b	CaSR	MAGE-D2	NCCT
Age of onset	Antenatal/newborn	Antenatal/newborn	Infancy	Antenatal/newborn	Antenatal/newborn	Infancy/child	Antenatal/newborn	Child/adults
Hyper-PGE2	++	++	±	++	++	−	+	−
Polyuria	++	++	±	++	++		++	+
Hypokalemia	+	+[a]	+	+	+	+	+	++
Hypochloremia	±	±	+	+	±	±	±	+
Hypomagnesemia	−	−	±	±	±	++	±	++
Hypercalciuria/nephrocalcinosis	++/++	++/++	±	±	±	++/+	±	−/−
Hypocalciuria	−	−	−	−	−	−	−	++
Growth failure	++	++	±	++	++	+	−	±
Chronic kidney disease	±	±	±	++	++	±	−	−
Sensorineural deafness	−	−	−	+	+	−	−	−
TALH	++	++	+	+	+	±[b]	++	−
DCT or CCD	−	+	+	+	+	+[b]	+	++
Pharmacological phenotypes	Furosemide	Furosemide/amiloride	Thiazide/furosemide	Thiazide/furosemide	Thiazide/furosemide	Thiazide	Thiazide/furosemide	Thiazide

[a]Initial hyperkalemia in the newborn. Later there is persistent hypokalemia. [b]Affects both TALH and DCT but predominantly affects DCT. All disorders manifest hypokalemia, alkalosis and hyperaldosteronism. ++, strong presence; +, presence; ±, variable occurrence or mild events; −/−, strong absence; −, absence; empty box indicates unknown event.
BSDN, Bartter's syndrome with sensorineural deafness; hyper-PGE2, elevated PGE2 in serum or urine.

presentation, characterized by polyhydramnios, extreme prematurity and hypovolemia in the newborn (Table 1 and Figures 1–3) [22–24, 37, 67, 68]. Unlike types I and II BS, hypercalciuria is often self-limiting and medullary nephrocalcinosis is absent. There is a common progression to end-stage kidney disease [69]. Also, a deficiency of chloride transport in the scala media of the inner ear produces concurrent sensorineural deafness [63, 67–69].

BS type V, as produced by autosomal dominant hypocalcemia (ADH), results from inactivation of luminal NKCC2 on TALH and of basolateral sodium–calcium exchanger (NCX1) on the DCT. It represents a gain-of-function mutation of *CaSR*, the gene responsible for the CaSR (Figures 1 and 2) [5, 70]. A concomitant reduction in paracellular Ca^{2+} absorption is the consequence of decreased lumen-positive PD and the greater availability of calcium-dependent claudin-14 (Figure 1) [30, 31, 70]. Also, recently classified as type V BS is an X-linked mutation in MAGE-D2 that encodes melanoma-associated antigen D2 (MAGE-D2; essential for fetal expression of NKCC2 and NCCT) [71, 72]. Given the different mechanisms, it may be more appropriate to classify this entity as type VI BS. In one study, perinatal death occurred in about one-third of 13 affected pregnancies, while paradoxically, the surviving infants manifested with self-limiting polyuria and hypokalemic alkalosis [72].

Pseudo-BS

Pseudo-BS presents as hypokalemic metabolic alkalosis, typically in the clinical context of extrarenal salt losses (Table 2). It consists mostly of gastrointestinal disorders such as infantile hypertrophic pyloric stenosis, congenital chloridorrhea and certain eating disorders (EDs). It may also result from excessive cutaneous losses of NaCl in CF. The relationship of these disorders with BS and GS will be discussed in order of their clinical presentation from infancy to adulthood. Although we give prominence to certain topics for their educational values, unlike EDs, most of these disorders are rare.

Infantile hypertrophic pyloric stenosis. Infantile hypertrophic pyloric stenosis (IHPS) is a potentially life-threatening disorder of young infants. It is far more common than BS. As in perinatal BS, there is a predisposition for (atypical) presentation in premature infants [66, 73]. Affected infants may present with projectile, nonbilious vomiting and an abdominal mass arising from hypertrophy of the pyloric sphincter [74]. Loss of gastric acid results in hypochloremia and secondary hyperaldosteronism produces hypokalemia (Table 2 and Figure 4) [8, 74]. Diagnostic urinary chloride is often <20 mEq/L, while the value is >20 mEq/L in BS (Figure 4) [75]. Mimicking the presentation of antenatal BS is a rare report of an early-onset IHPS in association with prematurity and polyhydramnios [76].

Congenital chloride diarrhea. Congenital chloride diarrhea (CCD) is a rare AR disorder that is marked by persistent secretory diarrhea in early infancy [77]. The defective gene is *SLC26A3*, which encodes a chloride/bicarbonate exchanger that occurs on the brush border membranes of ileal and colonic epithelia [77]. Dehydration and hypokalemic hypochloremic alkalosis are common (Table 2 and Figure 4). As in polyuria of BS, an extreme watery stool may soak the diaper of an affected infant [78]. Unlike the second-trimester event (26–30 weeks) in BS, polyhydramnios in CCD presents after 35 weeks of gestational age [78, 79]. Fetal ultrasonography shows megacolon in CCD while megabladder occurs in BS [80, 81]. In contrast to elevated

Table 2. Comparison of clinical, biochemical and diagnostic features in pseudo-BS variants, BS and GS

Pseudo-BS versus BS and GS	Idiopathic hypertrophic pyloric stenosis	Congenital chloride diarrhea	CF	Purging behavior	BS	GS
Clinical manifestations	Projectile vomiting, severe dehydration and epigastric mass	Watery diarrhea and severe dehydration	Meconium ileus, mal-absorption, dehydration and pulmonary disease	Vomiting, Russell's sign, subconjunctival bleeding and sialadenosis	Polyhydramnio, dehydration, FTT and CKD	Asymptomatic, muscle cramp, fatigue and hypokalemic paralysis
Gene variants association	Polygenic; BARX1 and EML4-MTA3	SLC26A3	CFTR (ΔF508)	None	SLC12A1, CLCNKA, CLCNKB, BSND, KCNJ1, CASR and MAGED2	SLC12A3
Age of onset	Post-natal 4–6 weeks	Antenatal/early infancy	Early infancy/ childhood	Adolescent/young adults	Antenatal/ early infancy/childhood	Late childhood/ young adults
Polydipsia	None	Yes/no	None	None	Yes	Yes/no
Polyuria	None	None	None	None	Yes	Yes/no
Hyperaldosteronism	Yes	Yes	Yes	Yes	Yes	Yes
Hypokalemia	Yes	Yes	Yes	Yes	Yes	Yes
Hypochloremia	Yes	Yes	Yes	Yes	Yes	Yes
Hyponatremia	Yes/no	Yes	Yes	Yes	Yes/no	Yes/no
Hypercalciuria/nephrocalcinosis	No	No	No	Yes/no	Yes	No
Growth failure/weight loss	Yes	Yes	Yes	Yes	Yes	Yes/no
Urine chloride	Low	Low	Low	High/low	High	High
Diagnostic clues	Abdominal ultrasound	Fecal chloride >90 mmol/L	Sweat chloride/gene variant	Psychosomatic	Electrolyte pattern/ gene variant	Electrolyte pattern/ gene variant

FTT, failure to thrive; CKD, chronic kidney disease.

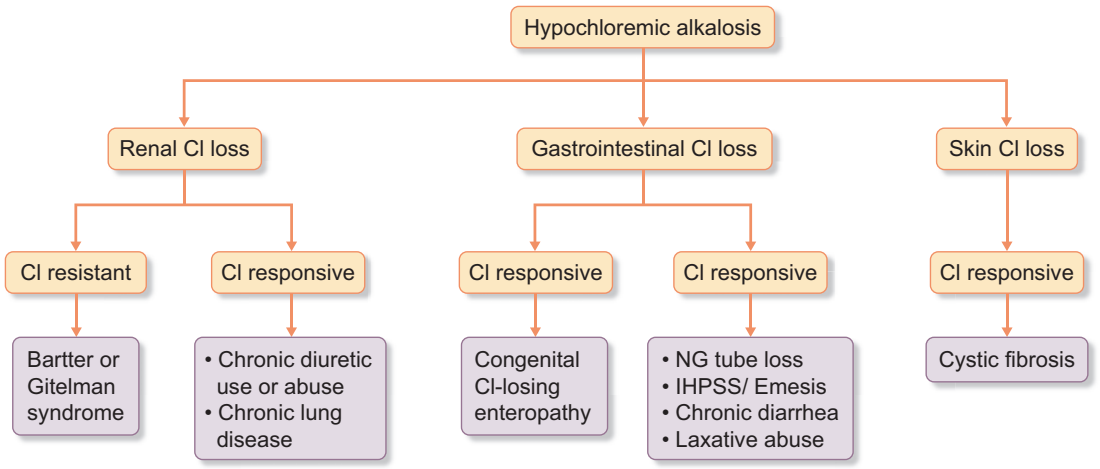

FIGURE 4: Algorithm for the Differential Diagnosis of Hypochloremic Metabolic Alkalosis.

urinary chloride in the fetus (amniotic fluid) or newborn with BS, a finding of fecal chloride >90 mmol/L is diagnostic in CCD [77–79].

EDs/purging behavior. EDs are the main differential diagnoses of BS and GS in adolescents and adults. They may result in life-threatening electrolyte derangements and are associated with a substantial cost of hospitalization [82, 83]. Differences in the electrolyte pattern are observed in the clinical subtypes of EDs. Surreptitious vomiting is the most frequent form. Due to gastric chloride depletion and volume contraction, there is severe hypokalemic alkalosis associated with low urinary chloride (Table 3 and Figure 4) [8, 84, 85]. Laxative abuse, the second most common form, results most frequently from the consumption of enteric stimulants that produce a large volume of watery diarrhea [80, 81, 86]. Unlike metabolic acidosis in diarrhea of short duration, the chronic diarrhea resulting from laxative abuse leads to hypokalemic alkalosis in response to secondary aldosteronism [7, 8, 80, 81, 86]. Although furosemide abuse is the least common purging behavior, it may also occur in the context of surreptitious vomiting, thereby worsening the hypokalemic alkalosis [75, 84]. Due to a common event of salt wasting, differentiation of diuretic abuse and BS and GS may be challenging. Unlike the steady elevation of urine chloride in BS and GS, chloride losses wax and wane on day-to-day urinary assessment among individuals with diuretic misuse [75, 87]. Furthermore, as in the stool analysis for laxatives, urine toxicology may reveal the offending diuretic substance (Table 4) [80]. Due to extrarenal salt loss, surreptitious emesis and laxative abuse are termed pseudo-BS, while the appropriate designation for diuretic abuse is Bartter-like disorder (Tables 2 and 3, Figure 4). There are distinct physical stigmata of purging behavior. Russell's sign is scarring on the back of the hands that results from repeated scraping against the upper teeth. There may be subconjunctival hemorrhage and swollen parotid glands [81, 86, 88, 89]. Although its presentation in types I and II BS occurs in infancy, there may be adult-onset medullary nephrocalcinosis in chronic diuretic abuse [89]. Unlike the absence of kidney stones, because of persistent polyuria, in BS, laxative abuse increases the likelihood of ammonium urate urolithiasis [90]. Finally, with a report of concurrent hypokalemic alkalosis both in newborn infants (pseudo-BS) and in their mothers, Bartter-like events may complicate chronic diuretic abuse in pregnant women [91, 92].

CF. CF is an AR disorder that results from mutations of the gene that encodes CFTR, a chloride-conducting channel that regulates anion transport and optimizes mucociliary clearance in the airways [93, 94]. Up to 90% of patients with CF have at least one copy of the F508del mutation on chromosome 7 [93]. Depending upon the severity of CFTR dysfunction, a consequence of the specific gene mutation, clinical presentation in affected individuals varies widely [93, 94]. Mimicking BS, children <2 years of age who reside in a hot climate environment may present initially with isolated hypokalemic hypochloremic alkalosis (Table 2 and Figure 4) [95, 96]. Indeed, communities that lack laboratory facilities for sweat testing have used paradoxical findings of metabolic alkalosis in infants with diarrhea as a criterion for the empirical diagnosis of CF [97]. The absence of a regulatory function of CFTR on the renal apical ROMK channel may explain the findings of isolated hypokalemic alkalosis (pseudo-BS) in some patients (Figure 3) [20, 21, 98]. Interestingly, there are reports of the common occurrence of isolated *CFTR* mutations including T338I, D110E, D110H and 711+1G>T/IVS8-5T in pseudo-BS [98–101].

GS. GS is an AR disorder resulting from mutations of the *SLC12A3* gene [102, 103]. As a reflection of the absent NCCT activity in GS, it may also be described as a pure thiazide-like phenotype [4, 5]. Although reasons for the milder clinical expression of GS are incompletely understood, they may include a lower fraction of salt reabsorption by the NCCT in early DCT compared with the NKCC2 in TALH (6% versus 25%) [14, 15, 33]. GS is often asymptomatic in childhood, while fatigue, salt craving, cramps and tetany may be evident in young adults [102, 104, 105]. Occasionally its diagnosis may be a fortuitous

Table 3. Comparison of clinical, biochemical and diagnostic features in Bartter-like syndrome and BS and GS

Bartter-like versus BGS	Drug-induced BS	Cystinosis	Dent disease	Sjögren syndrome	Chronic diuretic abuse	BS	GS
Clinical findings	Sepsis, antibiotic and dehydration	Fanconi syndrome, photophobia, rickets and hypothyroidism	Low molecular weight proteinuria, Fanconi syndrome, nephrocalcinosis, hypokalemia, hypercalciuria, and CKD	Rheumatic disease, xerostomia, kerato-conjunctivitis sicca	Vomiting, dehydration, Russell's sign, sub-conjunctival bleeding and sialadenosis	Polyhydramnios, dehydration, FTT and CKD	Asymptomatic, muscle cramp, fatigue and hypokalemic paralysis
Gene variants association	None	CTNS	CLCN5 and OCRL1	None	None	SLC12A1, CLCNKA, CLCNKB, Barttin, KCNJ1, CASR and MAGED2	SLC12A3
Age of onset	All age groups	Early infancy/childhood	Childhood	Adults	Adolescents/young adults	Antenatal/early infancy/childhood	Late childhood/young adults
Polydipsia	Yes/no	Yes	Yes/no	Yes/no	Yes/no	Yes	Yes/no
Polyuria	Yes	Yes	Yes/no	Yes/no	Yes	Yes	Yes/no
Hyperaldosteronism	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hypokalemia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hypochloremia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hyponatremia	Yes/no	Yes	Yes	Yes/no	Yes	Yes/no	Yes/no
Hypercalciuria/nephrocalcinosis	Yes, hyper-calciuria/no, nephrocalcinosis	No	Yes	No	Yes/no	Yes	No
Growth failure/weight loss	Yes	Yes	Yes	Yes	Yes	Yes	Yes/no
Urine chloride	High	High	High	High	High/low	High	High
Diagnostic clues	Acquired BS with aminoglycoside use	Fanconi syndrome/elevated leucocyte cystine	CKD/Lowe syndrome/gene variant	SSA antibody	Psycho-somatic	Electrolyte pattern/gene variant	Electrolyte pattern/gene variant

FTT, failure to thrive; CKD, chronic kidney disease.

Table 4. Comparison of clinical, biochemical and diagnostic features in purging behavior variants, BS and GS

Purging behavior versus BS and GS	Surreptitious vomiting/ bulimia	Acute laxative abuse	Chronic laxative abuse	Chronic diuretic abuse	BS	GS
Clinical findings	Vomiting, dehydration, Russell's sign, subconjunctival bleeding and sialadenosis	Normal physical, diarrhea and dehydration	Other signs of ED, weight loss, dehydration, constipation and edema	Other signs of ED, weight loss, dehydration and edema	Polyhydramnios, dehydration, FTT and CKD	Asymptomatic, muscle cramp, fatigue and hypokalemic paralysis
Age of onset	Adolescents/young adults	Adolescents/young adults	Adolescents/young adults	Adolescents/young adults	Antenatal/early infancy/ childhood	Late childhood/young adults
Hyperaldosteronism	Yes	Yes	Yes	Yes	Yes	Yes
Hypokalemia	Yes	Yes	Yes	Yes	Yes	Yes
Hypochloremia	Yes	No (acidosis)	Yes	Yes	Yes	Yes
Hyponatremia	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no
Hypercalciuria/nephrocalcinosis	No	No	No	Yes/no	Yes	No
Growth failure/weight loss	Yes	Yes/no	Yes	Yes	Yes	Yes/no
Urine chloride	Low	Low	Low	High/low	High	High

FTT, failure to thrive; CKD, chronic kidney disease.

event arising from an incidental discovery of subtle laboratory changes [3, 102]. More serious clinical events in older age are hypokalemic rhabdomyolysis, periodic paralysis, seizures and cardiac arrhythmias [103–105]. The signature findings in GS are hypomagnesemia and hypocalciuria. Hypomagnesemia is due to the disruption of transcellular transport of magnesium, which ordinarily occurs through the apical TRPM6 (Figure 3) [106, 107]. On the other hand, hypocalciuria results from a compensatory increase in the PT passive reabsorption of calcium (coupled with sodium) in response to volume depletion in the DCT [107, 108]. Furthermore, absence of the apical NCCT creates an electrochemical gradient that favors a basolateral extrusion of Ca^{2+} in exchange for an intracellular moving Na^{+} (Figure 3) [5, 107, 108]. There is also an increase in the abundance of TRPV5, a channel for calcium absorption on the DCT [106, 107].

Bartter- and Gitelman-like disorders

Unlike pseudo-BS, Bartter- and Gitelman-like disorders are due to urinary salt losses and are therefore indistinguishable from BS and GS (Table 3).

Renal tubular *claudin-10* gene mutation. Most recently, in four separate publications, there has been a description of an SLT that is easily confused with BS and GS. Therein a total of 22 patients presented with an age range of 4–53 years [109–112]. As a result of the deficiency of claudin-10b (*CLDN10* gene) in the tight junction of the TALH, these cases demonstrated impaired paracellular absorption of sodium [31, 109–112]. The resultant increase in sodium delivery at the DCT activates ENaC with a secondary loss of K^{+} and H^{+} [7, 8, 31, 112]. Due to a compensatory wider distribution of claudin-16 and -19 at the more distal TALH, there is an increase in paracellular absorption of Ca^{2+} and Mg^{2+}. Consequently there may be hypermagnesemia and nephrocalcinosis [28, 29, 31]. In addition, a deficit of claudin-10b involving the skin and salivary gland causes anhidrosis and xerostomia in early childhood. Presenting at an older age is hypokalemic alkalosis associated with variable events of hypocalciuria, hypercalciuria, hyposthenuria and loss of GFR [109–112].

Epilepsy, Ataxia, Sensorineural deafness and Tubulopathy (EAST) or Seizures, Sensorineural deafness, Ataxia, Mental retardation and Electrolyte imbalance (SeSAME) syndrome. EAST syndrome is a rare AR disorder that presents with infantile epilepsy, severe ataxia, sensorineural deafness, mental retardation and renal tubulopathy [113, 114]. Deficient expression of Kir4.1 potassium channel on the DCT, cochlear stria vascularis and glial cells of the brain results from mutations of the *KCNJ10* gene [113, 114]. The absence of basolateral potassium recycling suppresses the activity of the apical NCCT by the inhibition of WNK4 and WNK1 [115, 116]. An increase in distal sodium delivery to the late DCT activates secondary aldosteronism [7, 8, 117]. Neurological features often precede the childhood onset of a predominantly Gitelman phenotype, characterized by hypomagnesemia, hypocalciuria and hypokalemic alkalosis [118].

Drug-induced renal salt loss. Aminoglycosides cause self-limited inhibition of NaCl on the TALH and NCCT on the DCT [5, 119]. Multiple cases of aminoglycoside-associated hypokalemic and hypochloremic alkalosis, particularly in premature infants, have been reported in patients receiving gentamicin, netilmicin and amikacin (Table 3) [119–123]. With a mechanism similar to type V BS, these polyvalent cationic molecules enhance the

sensitivity of CaSR located on the basal membrane of the renal epithelial cells (Figures 1 and 2) [5, 76].

Hereditary PT defects

Cystinosis. Cystinosis is a rare AR disorder that results from mutations in the cystinosin lysosomal cystine transporter (*CTNS*) gene [124–126]. The kidney, cornea, bone marrow and thyroid may be involved in an age-dependent manner [124–126]. Typically the severe form of cystinosis presents in late infancy with Fanconi syndrome and growth failure [124–126]. Although the responsible mechanism is unclear, a defect in PT sodium transport associated with secondary aldosteronism in the early stage of disease may produce hypokalemic alkalosis instead of the conventional acidosis (Table 3) [124, 125, 127].

Dent disease. Dent disease is a rare X-linked recessive disorder of the renal PT that manifests as low molecular weight proteinuria, hypercalciuria, nephrocalcinosis and kidney stones [128]. Most frequently it results from the inactivation of the endosomal voltage-gated chloride–hydrogen ion exchanger ClC-5 [130]. Clinical manifestations are variable and may include Fanconi syndrome [81]. The reasons for its presentation as SLT are unknown (Table 3) [128–131].

Sjögren syndrome. In Sjögren syndrome (SS), multiple cases of a GS presentation have been reported (Table 3) [132–136]. These may occur in three clinical contexts: a concurrent manifestation of both disorders in a single patient, autoantibodies in SS producing inactivation of renal tubular cotransporters and autoantibodies in SS promoting the clinical expression of GS in an individual with a heterozygote gene mutation [132, 133]. It is important to differentiate these three entities, given the potential for a response to immunosuppression in the autoimmune variants [134]. The absence of immunohistochemical staining for NCCT on renal tissues and demonstration of its circulating antibody is suggestive of a diagnosis [133, 137]. Finally, genetic analysis is necessary to differentiate autoimmune GS from a genetic mutation of *SLC12A3* (GS) in a patient with a diagnosis of SS [133, 138].

CONCLUSION

Because of wide variations and the lack of specificity in clinical presentations, unrelated disorders may mimic SLT. Pseudo-BS occurs in nasogastric fluid losses, intractable emesis, pyloric stenosis, CF and EDs. Unlike BS, urine chloride excretion is low in pseudo-BS. As in BS and GS, renal salt wasting occurs in claudin-10b mutations, EAST syndrome, cystinosis, aminoglycoside toxicity and diuretic abuse. Finally, a relatively common event of heterozygous gene mutations for GS, particularly in the Caucasian population, increases the likelihood of its random occurrence in certain diseases of adult onset.

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CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part, except in abstract format.

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