
بسم الله الرحمن الرحيم

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Update In Bartter and Gitelman Syndromes

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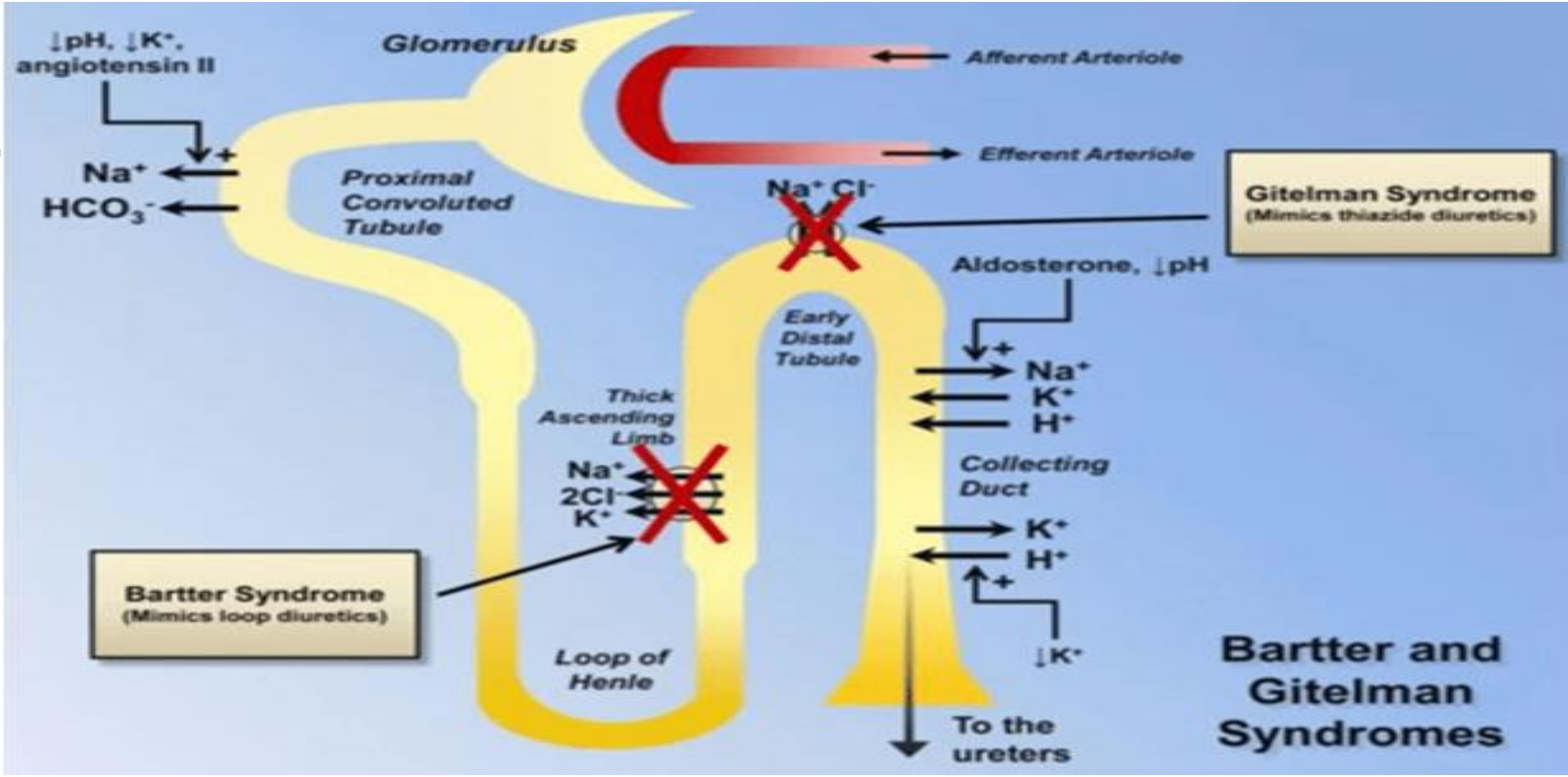
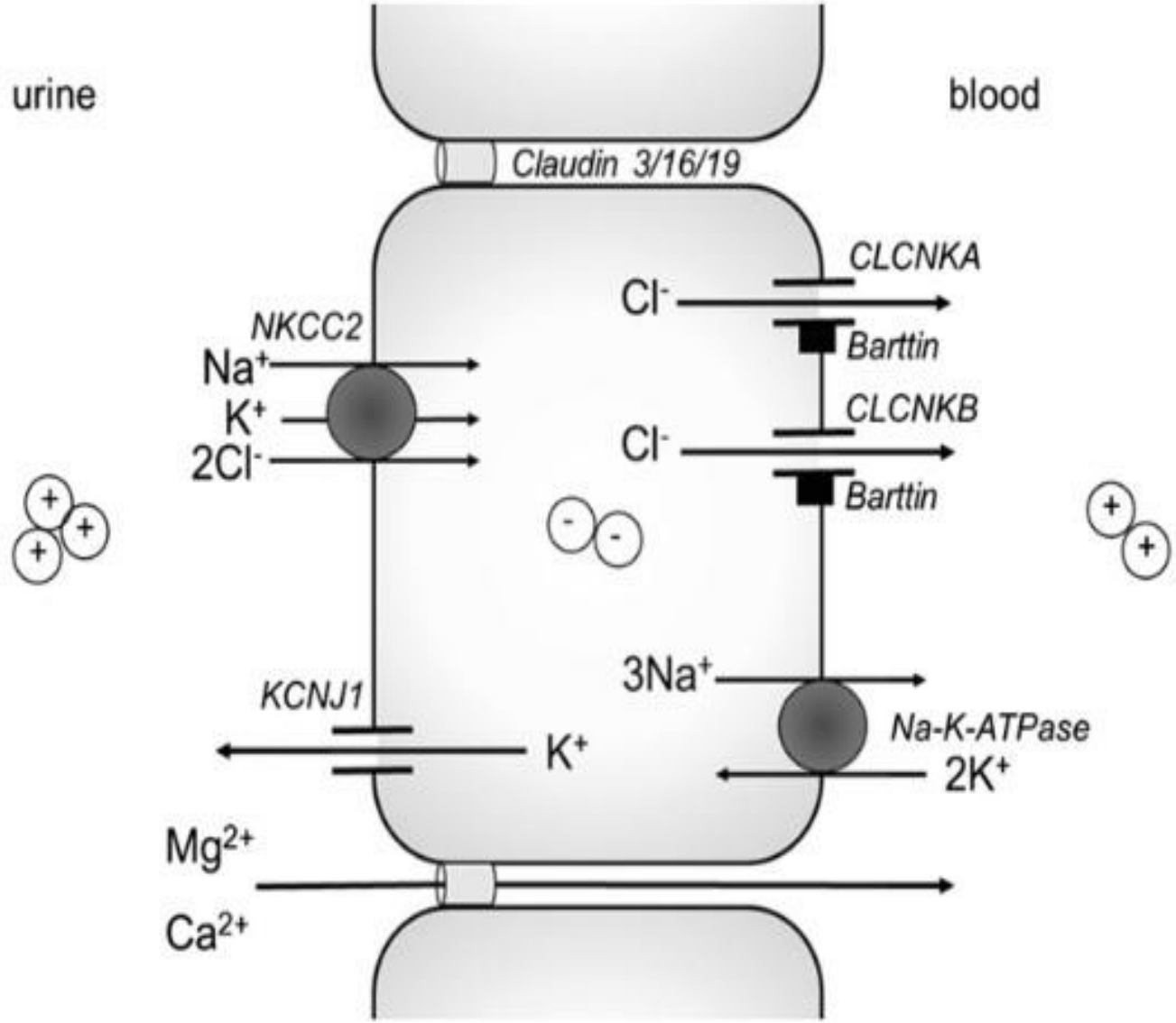

↓pH, ↓K+, angiotensin II
Glomerulus
Afferent Arteriole
Efferent Arteriole
Na+
HCO3-
Proximal Convoluted Tubule
Na+ Cl-
Gitelman Syndrome
(Mimics thiazide diuretics)
Aldosterone, ↓pH
Early Distal Tubule
Na+
K+
H+
Thick Ascending Limb
Na+
2Cl-
K+
Collecting Duct
K+
H+
↓K+
Bartter Syndrome
(Mimics loop diuretics)
Loop of Henle
To the ureters
Bartter and Gitelman Syndromes

Bartter and Gitelman syndromes are rare, recessively inherited tubular disorders which are associated with hypokalemia and hypochloremic metabolic alkalosis due to stimulation of the renin-angiotensin-aldosterone system by a primary defect in salt (NaCl) handling in the thick ascending limb and distal convoluted tubule, respectively

These disorders differ in terms of age of onset, severity, presence of urinary concentrating defect and/or hypomagnesemia, and magnitude of urinary calcium excretion, reflecting the tubular segment of origin


urine
blood
Claudin 3/16/19
CLCNKA
Cl-
Barttin
NKCC2
Na+
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CLCNKB
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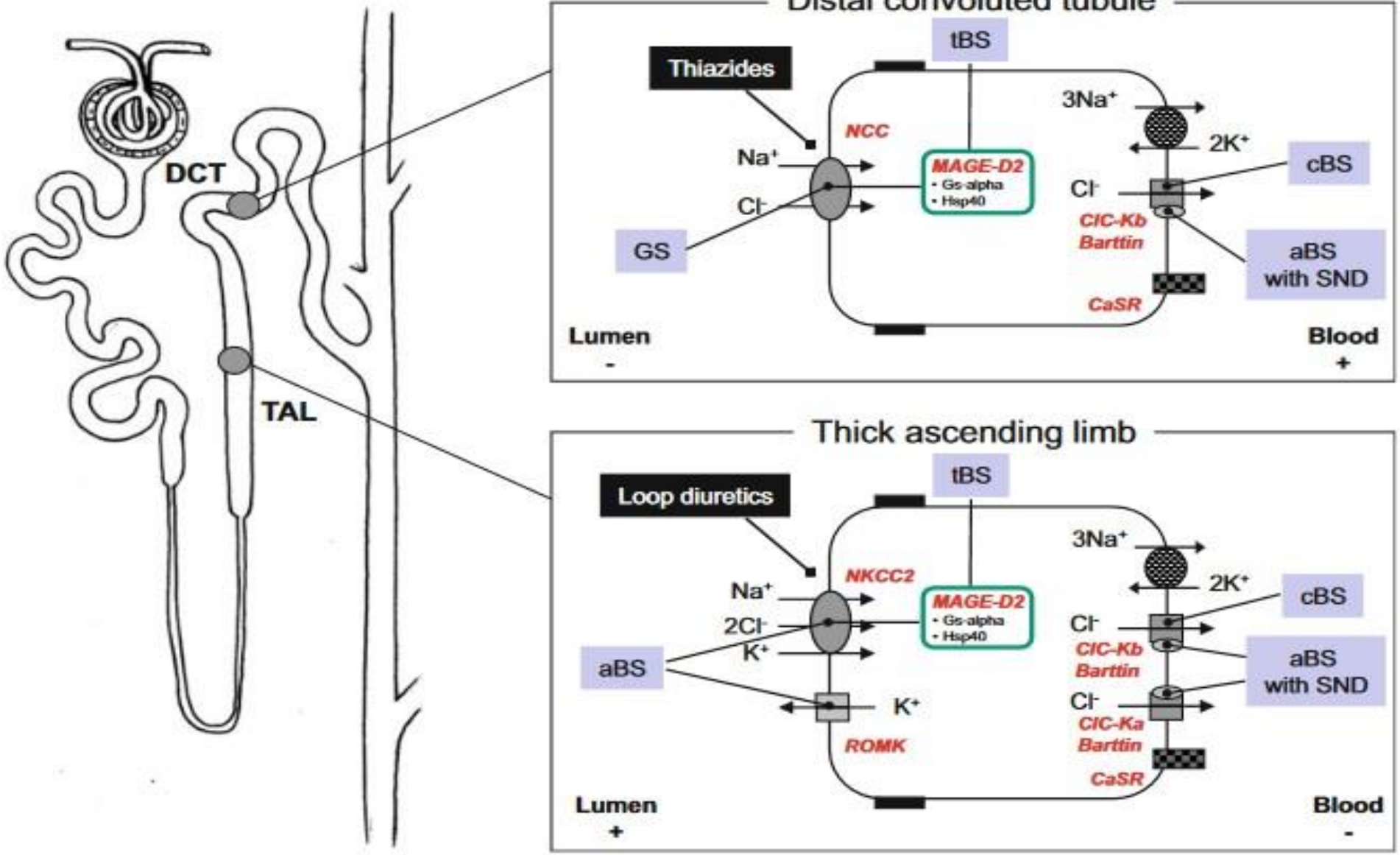
Barttin
3Na+
KCNJ1
K+
Na-K-ATPase
2K+
Mg2+
Ca2+


DCT
TAL
Distal convoluted tubule
tBS
Thiazides
NCC
3Na+
2K+
Na+
Cl-
MAGE-D2
• Gs-alpha
• Hsp40
cBS
Cl-
ClC-Kb
Barttin
GS
aBS
with SND
CaSR
Lumen
-
Blood
+
Thick ascending limb
tBS
Loop diuretics
NKCC2
3Na+
2K+
Na+
2Cl-
K+
MAGE-D2
• Gs-alpha
• Hsp40
cBS
Cl-
ClC-Kb
Barttin
aBS
aBS
with SND
K+
Cl-
ClC-Ka
Barttin
ROMK
CaSR
Lumen
+
Blood
-

Bartter syndrome (BS) was first described in 1962 by Frederic Bartter

Polyuria (which, depending on the subtype, can manifest antenatally with polyhydramnios and preterm birth)

Polydipsia

Muscle weakness ,growth retardation

hypokalaemia

hypochloraemic metabolic alkalosis

Increased urinary excretion of prostaglandins, high plasma renin activity, and a resistance to the pressor effects of exogenous angiotensin II

Elevated renin and aldosterone levels

Bart

Bartter syndrome type 1 (BS1):

Mutations in the gene encoding the luminal NKCC2 transporter

Bartter syndrome type 2 (BS2):

Mutations disrupting the function of the luminal KCNJ1 channel

BS1 and BS2 are often classified as antenatal BS

Clinical Manifestations
Antenatal Bartter Syndrome

Typical features of aBS type I (NKCC2) and typeII (ROMK) :

Polyhydramnios : within the second trimester of gestation

Premature delivery: (usually around 32 weeks)

Severe polyuria: lifethreatening episodes of dehydration

The polyuria can be massive (>20 mL/kg/h)

Hypercalciuria: leading to nephrocalcinosis within the first months of life

Activation of the RAAS

Magnesium wasting is not common in aBS

Failure to thrive and growth retardation are invariably observed

Peculiar facies : triangularly shaped face, prominent forehead, large eyes, protruding ears, and drooping mouth

Continue

Systemic manifestations : fever of unknown origin, diarrhea, vomiting, and generalized convulsions(systemic overproduction of PGE), and recurrent urinary tract infection

Osteopenia: high urinary excretion of bone resorption markers

Hypophosphatemia :with decreased tubular phosphate reabsorption possibly related to tubular damage and hypokalemic nephropathy

High Cl and aldosterone concentrations in the amniotic fluid

chronic kidney disease(CKD) : early neonatal events and dehydration episodes, hypokalemic nephropathy, nephrocalcinosis, and potential nephrotoxicity of nonsteroidal anti inflammatory drugs (NSAID)

transient hyperkalemia: during the first days of life (ROMK deficient patients)

Feature	Type I BS	Type II BS	Type IV BS	BS	Type V BS	(*SLC12A3*)
Age of onset	Antenatal	Antenatal	Antenatal	Variable	Antenatal, transient	Childhood (> age 6 years)
Maternal polyhydramnios	Present	Present	Present	Rare	Present, very severe	Absent
Prematurity	Present	Present	Present	Rare	Present	Absent
Polyuria	Present	Present	Present	Occasional	Present	Absent
Failure to thrive	Present	Present	Present	Common	Present	Absent
Growth retardation	Present	Present	Present (severe)	Common		Occasional
Spasm/tetany/ muscle weakness	Absent	Absent	Absent	Occasional		Present
Nephrocalcinosis	Present	Present	Absent	Rare	Rare	Absent
Sensorineural deafness	Absent	Absent	Present	Absent[a]	Present	Absent
Hypokalemic metabolic alkalosis	Present	Present (transient neonatal hyperkalemia)	Present	Present	Present	Present
Plasma Mg^{2+}	Normal	Normal	Normal or low	Normal or low		Low
Urinary Ca^{2+} excretion	High	High	Moderate (transient) or normal	Usually normal	High	Low
Urinary NaCl excretion	High	High	Very high	Variable increase	High	Mild increase
Maximal urine osmolality	Hyposthenuria	Hyposthenuria	Iso-/ hyposthenuria	Usually normal		Normal
High renin/ aldosteronism	Present	Present	Present	Present	Present	Present
Urinary PGE2 excretion	High	High	High	High		Normal

Differential Diagnosis

1- PHA1 is characterized by permanent hyperkalemia with metabolic acidosis, whereas type II aBS patients typically have metabolic alkalosis, as well as hypercalciuria and nephrocalcinosis

2- Nephrogenic diabetes insipidus :The urinary concentrating defect is so severe that it can lead to hypernatremia

3-Medullary nephrocalcinosis, incomplete distal renal tubular acidosis: Some patients with aBS may lack metabolic alkalosis during the first year of life or even present a transient metabolic acidosis with defective urinary acidification

Treatment

Indomethacin starting 4–6 weeks after birth(0.5 mg/kg/day to 2.5 mg/kg/day)

Reduces polyuria, improves hypokalemia, normalizes plasma renin levels, and reduces hypercalciuria

The ROMK-deficient patients are particularly sensitive to indomethacin, with doses well below 1 mg/kg/day sufficient to maintain normal plasma K+ levels

COX-2 selective inhibitor rofecoxib : significant suppression of PGE2 and correction of hyperreninemia

K + supplementation

K +sparing diuretic

Angiotensin converting enzyme (ACE) inhibitors

Thiazide??

Case Reports

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Late-Onset Bartter Syndrome Type II Due to a Homozygous Mutation in *KCNJ1* Gene: A Case Report and Literature Review

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 31-year-old
Final Diagnosis: Bartter syndrome
Symptoms: Weakness
Medication: —
Clinical Procedure: —
Specialty: Genetics • Nephrology

Objective: Unusual clinical course
Background: Bartter syndrome is a rare genetic disease characterized by hypokalemia, metabolic alkalosis, and hyperrenin

Huang et al., 2014 [3]	35	Male	Incidental finding of nephrocalcinosis in lumbar spine X-ray done for low back pain	– Potassium: 2.8 mmol/l – Creatinine: 122 umol/l – 24-hour calcium excretion: 4.34 mmol/day	A homozygous missense mutation	c.658C>T	p.Leu220Phe	Potassium supplementation and spironolactone
Gollasch et al., 2017 [4]	43	Female	Incidental finding of nephrocalcinosis in ultrasound done during pregnancy	– Potassium: 2.8 mmol/l – Creatinine: 97 umol/l – 24-hour calcium excretion: 7.5 mmol/day	A compound heterozygous missense mutation	c.197T>A (novel mutation) c.875G>A	p.Ile66Asn p.Arg292Gln	Potassium supplement and angiotensin-converting-enzyme inhibitors (ramipril)
Li et al., 2019 [5]	34	Female	Weakness. persistent polyuria and polydipsia; weight and height were normal	– Potassium: 2.4 mmol/l – Creatinine: 97 umol/l – 24-hour calcium excretion: 6.9 mmol/day	A compound heterozygous missense mutation	c.701C>T (novel mutation) c.212C>T	p.The234Ile p.Thr71Met	Potassium supplementation
Sharma et. al., 2011 [6]	8.5	Female	Persistent polyuria and polydipsia; fifth percentile for weight and height	– Potassium: 2.5 mmol/l v Creatinine: 44 umol/l – Ca/creatinine 0.91 mg/mg (normal \0.2)	A novel compound heterozygous mutation	c.268G>T c.632T>G	p.Gly90Trp p.Ile211Ser	Potassium supplementation and nonsteroidal anti-inflamma-tory drugs (NSAIDs)
Present case	26	Male	Weakness. persistent polyuria and polydipsia; weight and height were	– Potassium: 1.7 mmol/l – Creatinine: 96 umol/l – 24-hour calcium excretion: 3.5 mmol/day	A homozygous missense mutation	c.658C>T	p.Leu220Phe	Potassium supplement and Aldosterone antagonists

Bartter syndrome type 3 (BS3)

classical BS

Defective function of the basolateral chloride channel CLCNKB (TAL and the DCT)

Affected children are usually born at term

Most patients have episodes of hypokalemic alkalosis and dehydration

Muscular hypotonia and lethargy during the first years of life

Increased urinary excretion of PGE2

Most patient show failure to thrive and growth retardation due to profound growth hormone deficiency

Osteopenia with increased markers of bone resorption

low plasma Cl and severe hypokalemic alkalosis , Increased plasma renin levels, with high or inappropriately normal aldosterone Levels

- Iso/hyposthenuria was only evidenced in approximately one-third of patients, whereas some achieved urinary osmolality above 700 mOsm/kg
- Only ~20% of patients had sustained hypercalciuria
- Mild hypophosphatemia, which could be related to tubular damage and hypokalemic nephropathy
- Half of the patients lacking ClC-Kb have hypomagnesemia
- Kidney failure in BS : salt wasting (including longstanding hypokalemia, hypovolemic episodes, or nephrocalcinosis), chronic activation of the RAAS with ensuing stimulation of TGF-beta and/or TNF-alpha, and toxicity of NSAID
- kidney cysts : K + wasting and secondary aldosteronism

Differential Diagnosis

- Use of loop diuretics, laxative abuse
- Chronic vomiting
- Generalized dysfunction of the proximal tubule (renal Fanconi syndrome), for instance, due to cystinosis , or Kearns-Sayre syndrome, a mitochondrial cytopathy caused by large deletions in mitochondrial DNA
- Familial kidney dysplasia
- Cystic fibrosis are prone to develop episodes of hyponatremic, hypochloremic dehydration with metabolic alkalosis
- Administration of prostaglandins in neonates with a ductus-dependent congenital cardiopathy , aminoglycosides or combined chemotherapy
- Partially empty sella detected by MRI

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

Treatment

- ✓Potassium supplementation (usually KCl, 1 to 3 mmol/kg/d)
- ✓Spironolactone (1 to 1.5 mg/kg/d)
- ✓Indomethacin: the first 4 years of life at doses ranging from 1 to 2.5 mg/kg/d
- ✓Rofecoxib
- ✓ACE inhibitor
- ✓Growth hormone deficiency : Recombinant human hormone treatment

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

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CASE REPORT

Clinical Case Reports Open Access WILEY

Genetic diagnosis of Bartter syndrome in Iranian patients and detection of a novel homozygous *CLCNKB* mutation

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Abstract

An Iranian girl with clinical symptoms of Bartter syndrome like hypokalemia, polyuria, polydipsia, hyponatremia, and hypochloremic alkalosis was referred to us in whom the *CLCNKB* gene was genetically evaluated using Sanger sequencing. A homozygous pathogenic variant of c.1332_1335delCTCT was detected in this patient

Najafi *et al. Orphanet Journal of Rare Diseases* (2019) 14:41
https://doi.org/10.1186/s13023-018-0981-5

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Mimicry and well known genetic friends: molecular diagnosis in an Iranian cohort of suspected Bartter syndrome and proposition of an algorithm for clinical differential diagnosis

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Age range of patients : 3 months to 6 years and all patients showed hypokalemic metabolic alkalosis

3 patients additionally displayed hypercalciuria, with evidence of nephrocalcinosis in one case

Screening by Whole Exome Sequencing (WES) and long range PCR revealed that 12/17 patients (70%) had a deletion of the entire CLCNKB gene

4/17 individuals (approximately 25% of cases) : pseudo-Bartter syndrome resulting from congenital chloride diarrhea due to a novel homozygous mutation in the SLC26A3 gene, Pendred syndrome due to a known homozygous mutation in SLC26A4, Cystic Fibrosis (CF) due to a novel mutation in CFTR and apparent mineralocorticoid excess syndrome due to a novel homozygous loss of function mutation in HSD11B2 gene

1 case (5%) remained unsolved

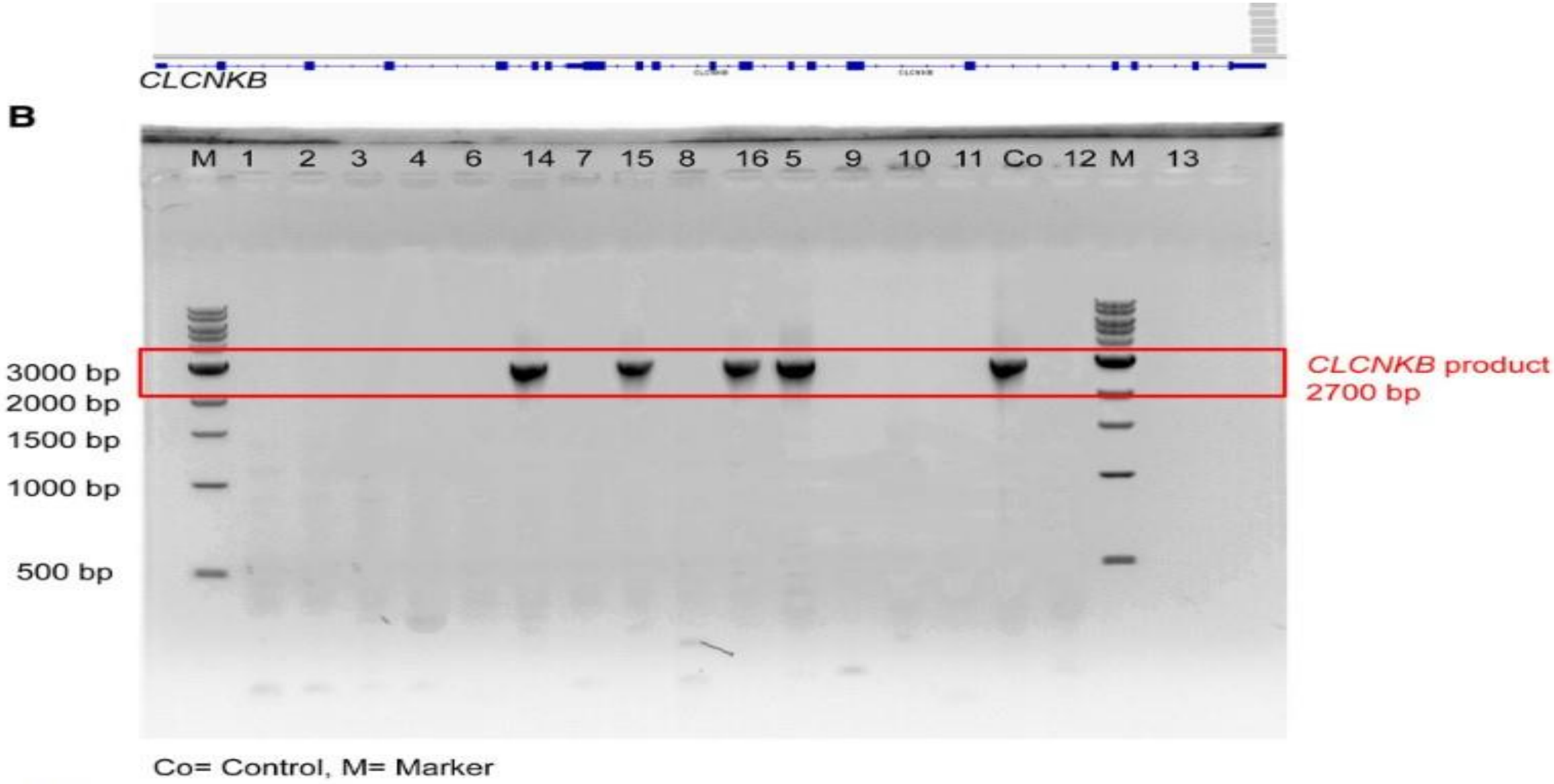


Fig. 1 (See legend on next page.)

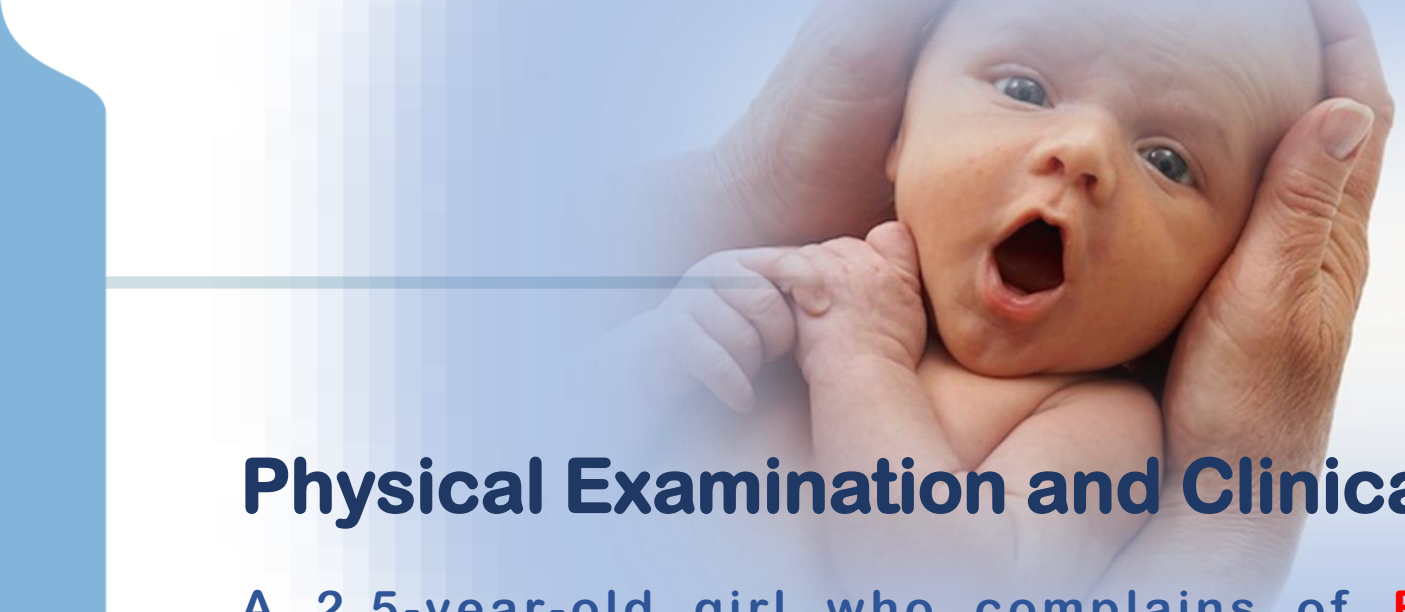
Bartter syndrome type 4 (BS4a,b)

Bartter syndrome type 4a (BS4a) is caused by disrupting mutations in the gene encoding

Barttin, a subunit of the basolateral chloride channels CLCNKA and CLCNKB

Type 4b (BS4b) is caused by simultaneous mutations in genes encoding both CLCNKA and CLCNKB, giving a phenotype similar to BS4a

- ✓Polyhydramnios and premature birth (antenatal BS)
- ✓Patients can have hypercalciuria and nephrocalcinosis
- ✓Moreover hypomagnesemia
- ✓Both these subtypes of BS have sensorineural deafness, since both chloride channels and their Barttin subunit are expressed in the inner ear
- ✓Deafness only occurs if function of both types of chloride channels is impaired



Physical Examination and Clinical Investigation:

A 2.5-year-old girl who complains of FTT and lethargy and vomiting, polyuria and dehydration, irritability referred to nephrology clinic and initial diagnosis for more evaluation and possible treatment done.

LOC: lethargic, hypotonic, not responding to sound/Febrile ×/Toxic ×

Weight: 6.5 Kg<3% L: 79 cm<3%

H&N: bilateral sensorineural deafness

Chest: normal

Abd: normal

- Lab data:

metabolic alkalosis (pH7.6)

hypokalemia(2.9 mEq/l)

hyponatremia.(123mEq/l)

serum Mg was normal (2.5)

BUN=49

Creatinine=1.2

Ca=9.8

P=4.2

urinary loss of chlorine (80 mmol/lit)

Hypercalciuria

serum aldosterone levels were high (1050 ng/lit) normal range 50-800 ,

renin 20(<11.2) urine K =52

Bartter syndrome (BS5)

Transient , severe antenatal form of X-linked BS

Mutations in the gene encoding the protein melanoma-associated antigen D2 (MAGE-D2)

Severe polyhydramnios causing premature birth

Can be hypercalciuria, hypermagnesuria and nephrocalcinosis

Symptoms resolve after the first weeks of life

Type-5 Bartter syndrome presenting with metabolic seizure in adulthood

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SUMMARY

Bartter syndrome is a very rare and heterogeneous disease with variable age of onset and symptom severity. Genotypically they have inherited disorders of the thick ascending limb in the renal tubular system, which manifest phenotypically as electrolyte imbalance due to loss of sodium, chloride and potassium. Gain of function mutations in the calcium-sensing receptor has been described in some patients with Bartter's syndrome (type-5 Bartter syndrome or autosomal dominant hypocalcaemia with Bartter syndrome) associated with hypocalcaemia and hypercalciuria differentiating it from Gitelman syndrome. This phenotype has been reported to present in adulthood with metabolic abnormalities. We present a case of a middle-aged woman who presented with metabolic seizures and on evaluation was found to have profound electrolyte abnormalities which were corrected with supplements and led to the resolution of symptoms.

INVESTIGATIONS

Laboratory analysis revealed normal haemogram, normal renal function and a normal thyroid profile. Liver function test revealed mild transaminitis and hypoalbuminemia. Electrolye analysis revealed hypokalaemia, hyponatraemia, hypocalcaemia, hypomagnesaemia and hypophosphatemia (table 1). Arterial blood gas analysis suggested metabolic alkalosis (pH of 7.48 and bicarbonate of 32 mEq/L). During the evaluation of the cause of dyselectrolaemia, patient denied any history of current or remote diuretic use. Urinary electrolytes were analysed (table 2). Urinary potassium was 120 mEq/g of creatinine excreted. Transtubular potassium gradient was 25. 52, suggesting urinary potassium loss. Twenty-four hours of urinary calcium was 344 mg/day. Serum vitamin D and serum parathyroid hormone levels were normal. Urinary chloride was 110 mmol/L. Our patient gave a history of dryness of mouth and in view of upper lobe fibrosis

Bartter-like subform of familial hypocalcaemia

Autosomal dominant or familial hypocalcaemia can be associated with hypokalaemic, hypochloraemic metabolic alkalosis

Before the discovery of MAGED2 mutations, referred to as Bartter syndrome type 5

Nowadays: caused by an activating mutation in the gene encoding the basolateral calcium-sensing receptor (CaSR).

Once activated, CaSR reduces the activity of KCNJ1, NKCC2, and the Na-K-ATPase, thereby causing a phenotype that can mimic BS

Bartter-like subform of familial hypocalcaemia

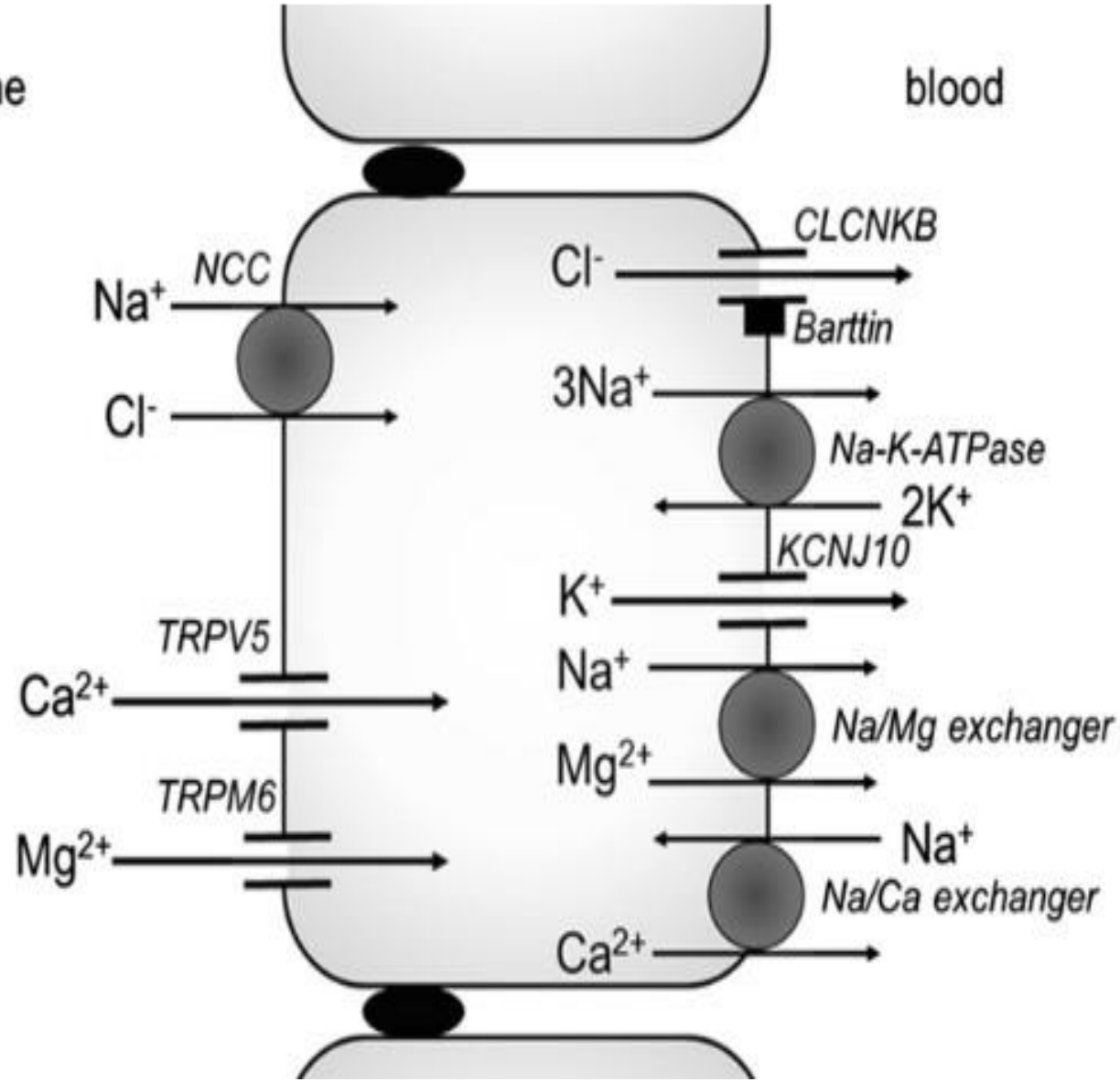
Symptomatic during adolescence or in adulthood

In contrast to patients with BS, who in general are normocalcaemic, patients with autosomal dominant hypocalcaemia usually present with symptomatic hypocalcaemia

Hypercalciuria causing nephrocalcinosis

CaSR activation decreases the activity of the basolateral potassium channel KCNJ10, which ensures the recycling of potassium over the basolateral membrane in order to maintain Na-K-ATPase activity

CaSR activation on the DCT can explain the hypomagnesemia that is often seen in patients with familial hypocalcaemia


urine
blood
NCC
Na+
Cl-
TRPV5
Ca2+
TRPM6
Mg2+
CLCNKB
Cl-
Barttin
3Na+
Na-K-ATPase
2K+
KCNJ10
K+
Na+
Na/Mg exchanger
Mg2+
Na+
Na/Ca exchanger
Ca2+

Gitelman syndrome (GS)

Gitelman syndrome (GS) was first described in 1966 by Hillel Gitelman

Mutations in the gene SLC12A3, encoding NCC and is inherited in an autosomal recessive

GS is exclusively a disorder of DCT

Patients typically present in late childhood or adulthood with

Hypokalaemic, hypochloraemic metabolic alkalosis and normal blood

pressure despit hyperaldosteronism

Key features: hypocalciuria with hypermagnesuria

Hypermagnesuria is caused by decreased expression of the luminal magnesium channel TRPM6 in cells lining the DCT due to cell dysfunction due to the mutations in NCC

Clinical Manifestations

The GS patients are often asymptomatic

Mild symptoms such as weakness, fatigue, salt craving, thirst, nocturia, constipation, or cramps.

Growth retardation and short stature, reflecting an alteration in the growth hormone-insulin-like growth factor I axis or pleiotropic effects resulting from magnesium depletion

Typical manifestations include muscle weakness, carpopedal spasms, or tetanic episodes triggered by hypomagnesemia

Blood pressure is reduced (Some adult patients with GS develop hypertension(40%)

chondrocalcinosis and sclerochoroidal calcifications : hypomagnesemia may promote the formation of calcium pyrophosphate crystals in joints and sclera

Higher bone mineral density : increased Ca 2+reabsorption and a decreased rate of bone Remodeling

- Prolonged QT interval : (~50% of the patient) increased risk for ventricular arrhythmias (Potassium and Mg2+ depletion)
- Hypokalemic rhabdomyolysis has been reported
- The prevalence of thyroid dysfunction was 4.4%
- Increased bacterial and fungal infections, increased prevalence of eczema/dermatitis and allergic disease, and the presence of autoimmune phenomena in 30%
- Impairs IL-17 responses, leading to immunodeficiency

- Vertigo without orthostatic hypertension was described in 22% ,vestibular disorder in 8%
- The expression of NCC in the medial part of the endolymphatic sac in the inner ear

Criteria for suspecting a diagnosis of GS

Chronic hypokalemia (<3.5 mmol/l) concomitant with inappropriate potassium wasting (spot urine, potassium /creatinine ratio >2.0 mmol/mmol [>18 mmol/g])

Metabolic alkalosis

Hypomagnesemia (<0.7 mmol/l [<1.70 mg/dl]); inappropriate magnesium wasting (fractional excretion of magnesium >4%)

Hypocalciuria (spot urine, calcium-creatinine ratio <0.2 mmol/mmol [<0.07 mg/mg]) in adults ,calcium-creatinine ratio in children should be interpreted according to age

High renin (activity or plasma levels)

Fractional excretion of chloride >0.5%

Normal or low BP

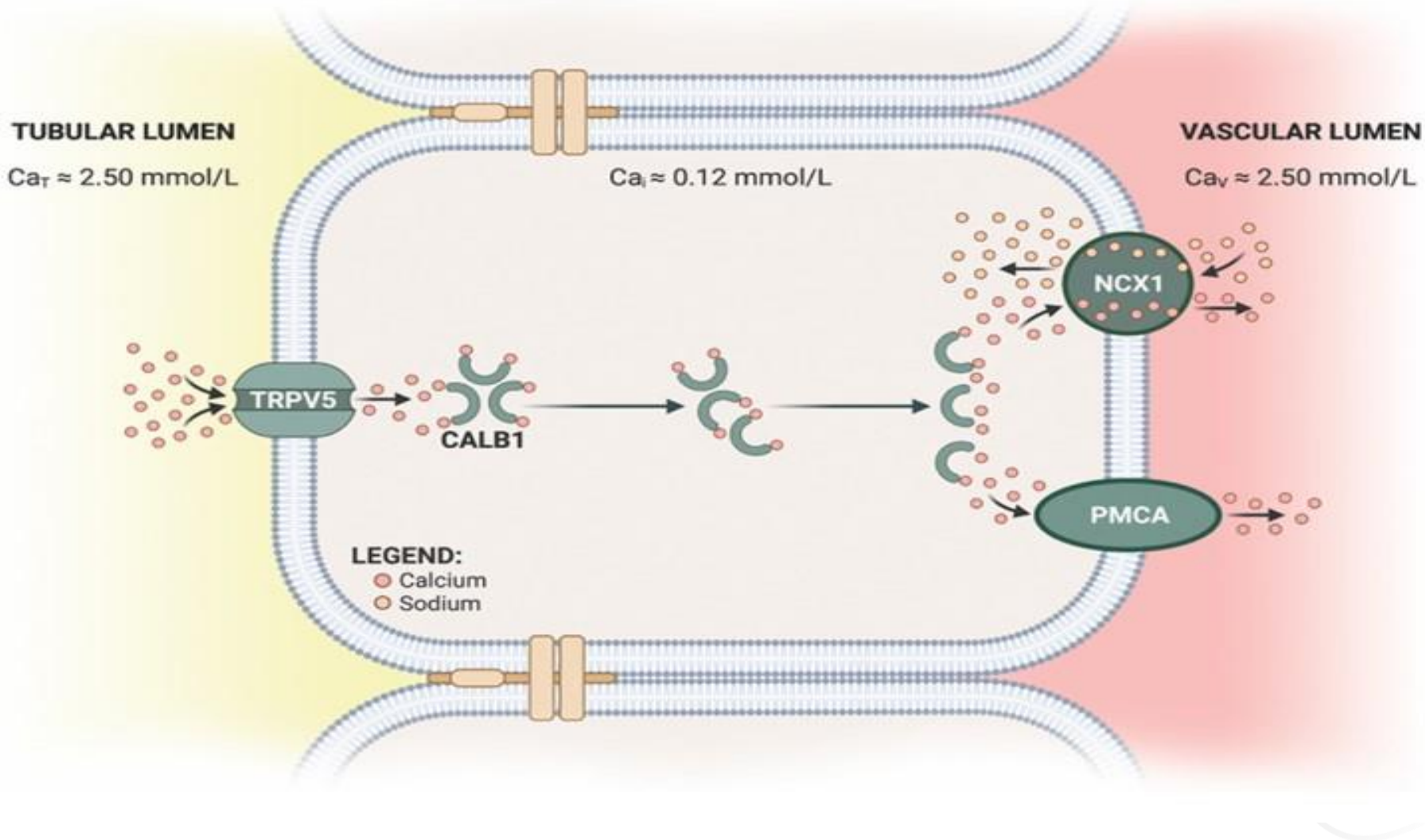
Normal renal ultrasound with absence of nephrocalcinosis or kidney abnormalities

The presence of both hypomagnesemia and hypocalciuria is highly predictive for the diagnosis of GS

Table 3 Clinical manifestations associated with Gitelman syndrome

Most common (> 50% of patients)	Prominent (20 to 50% of patients)	Occasional (Less than 20%)	Rare (Case reports)
Salt craving	Fainting	Early onset (before age 6)	Seizure
Cramps, muscle weakness, pain	Polyuria	Failure to thrive	Ventricular tachycardia
Fatigue	Arthralgia	Growth retardation	Rhabdomyolysis
Dizziness	Chondrocalcinosis	Vertigo, ataxia	Blurred vision
Nocturia	Prolonged corrected QT interval	Carpopedal spasm, tetany	Pseudotumor cerebri
Thirst, polydipsia	Febrile episodes	Vomiting	Sclerochoroidal calcifications
Paresthesia, numbness		Constipation	
Palpitations		Enuresis	
Low blood pressure		Paralysis	

Renal Ca and Mg handling in Gitelman syndrome



Hypokalaemic metabolic alkalosis				
Disorder	Gene	Protein	Inheritance	Differentiating features
BS Type I	*SLC12A1*	NKCC2 Co-transporter	AR	Antenatal or neonatal onset Nephrocalcinosis
BS Type II	*KCNJ1*	ROMK potassium channel	AR	Antenatal or neonatal onset Nephrocalcinosis
BS Type III	*CLCNKB*	ClC-Kb chloride channel	AR	Childhood onset Hypomagnesaemia, can have normocalciuria and phenocopy Gitelman Syndrome
BS Type IVa	*BSND*	Barttin subunit	AR	Neonatal onset Hypomagnesaemia, sensorineural deafness
BS Type IVb	*CLCNKA*	ClC-Ka Chloride Channel	AR	Neonatal onset Sensorineural deafness
BS Type V	*MAGED2*	MAGE-D2	XR	Antenatal or neonatal onset Transient
Gitelman Syndrome	*SLC12A3*	NCC co-transporter	AR	Childhood onset Hypomagnesaemia, hypocalciuria
Gitelman-like syndrome	*MT-TF* *MT-TI*	NCC co-transporter	Mt	Childhood onset Hyomagnasaemia, hypocalciuria
Gitelman-like syndrome	*RRAGD*	Rag GTPase D	AD	Hyomagnasaemia, nephrocalcinosis Dilated cardiomyopathy
East Syndrome	*KCNJ10*	Kir4.1	AR	Infancy CNS involvement
Helix Syndrome	*CLDN10*	Claudin-10b complex	AR	Childhood Hypermagnesaemia Exocrine gland dysfunction

Treatment

- ✓target for potassium :3.0 mmol/l and magnesium 0.6 mmol/l(1.46 mg/dl)
- ✓salt consumption (“salt craving”)
- ✓ Magnesium supplementation(Magnesium chloride, magnesium lactate, and magnesium aspartate):300 mg/day (12.24 mmol) of elemental magnesium (5 mg/kg in children, i.e.,0.2 mmol/kg)
- ✓ High doses of oral KCl supplements: (1–2 mmol/kg in children)
- ✓Eplerenone is a selective aldosterone antagonist, with significantly lower affinity for androgen, progesterone, and glucocorticoid receptors
- ✓Spironolactone
- ✓ indomethacin , rofecoxib

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Clinicopathological Features of Gitelman Syndrome with Proteinuria and Renal Dysfunction

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Novel SLC12A3 mutation in Gitelman syndrome

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SUMMARY

Gitelman syndrome (GS) is an autosomal recessive disease characterised by the presence of hypokalaemic metabolic alkalosis with hypomagnesaemia and hypocalciuria. The prevalence of this disease is 1–10/40 000. GS is usually associated with mild and non-specific symptoms and many patients are only diagnosed in adulthood. The disease is caused by mutations in the SLC12A3 gene. We present the case of a 49-year-old man referred to a nephrology appointment due to persistent hypokalaemia and hypomagnesaemia. Complementary evaluation revealed hypokalaemia, hypomagnesaemia, metabolic alkalosis, hyperreninaemia, increased chloride and sodium urinary excretion, and reduced urinary calcium excretion. Renal function, remainder serum and urinary ionogram, and renal ultrasound were normal. A diagnosis of GS was established and confirmed with genetic testing which revealed a novel mutation in SLC12A3 (c.1072del, p.(Ala358Profs*12)). This novel mutation extends the spectrum of known SLC12A3 gene mutations and further supports the allelic heterogeneity of GS.

(0.7–1.2 mg/dL); blood urea nitrogen 32 mg/dL (13–43 mg/dL). Arterial blood gas analysis showed metabolic alkalosis (pH 7.49; HCO_3 – 32.2 mmol/L; pCO_2 45 mm Hg). Further investigation revealed elevated plasma active renin (14.16 μU/mL; 1.6–3.2 μU/mL), normal aldosteronaemia (133.5 mg/mL; 10–160 mg/mL), hypocalciuria (92 mg/24 hours; 100–300), increased urinary excretion of sodium (315 mmol/24 hours; 40–220) and chloride (299 mmol/24 hours; 110–250) and inappropriately normal urinary excretion of potassium and magnesium. Estimated glomerular filtration rate [Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] was 102 mL/min/1.73 m^2. Renal ultrasound was normal, with no signs of lithiasis.

Based on the association of hypomagnesaemia, hypokalaemia, metabolic alkalosis and hypocalciuria, the diagnosis of GS was assumed. A genetic study was performed at Genomed laboratory after extraction of DNA from peripheral blood. Genetic analysis was conducted using oligonucleotide-based target capture (SureSelect, Agilent) followed

Case Report

SAGE Open Medical Case Reports

A novel mutation of *SLC12A3* gene causing Gitelman syndrome

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Abstract

A 48-year-old patient with a history of diabetes mellitus, presented to a surgical ward with abdominal pain. She was found to have hypokalemia. Her younger sister had passed away due to sudden cardiac death at the age of 25 years. Further evaluation revealed an elevated trans-tubular potassium gradient suggestive of renal potassium loss, normal blood pressure, hypomagnesemia, hypocalciuria, and alkalosis. Moreover, there was evidence of secondary hyperaldosteronism. Genetic studies revealed two heterozygous mutations of the *SLC12A3* gene, including a novel mutation which has not been reported before anywhere in the world. She was treated with intravenous potassium supplementation and was later converted to oral potassium and oral magnesium supplementation with spironolactone. Her potassium and magnesium levels normalized and glycaemic control also improved. Hypokalemia and hypomagnesemia found in Gitelman syndrome may be associated with insulin resistance and correction of electrolytes can lead to better glycaemic control.

Identification of compound mutations of *SLC12A3* gene in a Chinese pedigree with Gitelman syndrome exhibiting Bartter syndrome-liked phenotypes

Bingzi Dong[1†], Ying Chen[1†], Xinying Liu[2], Yangang Wang[1], Fang Wang[1], Yuhang Zhao[1], Xiaofang Sun[1] and Wenjuan Zhao[1*]

Abstract

Background: Gitelman syndrome is a rare salt-losing renal tubular disorder associated with mutation of *SLC12A3* gene, which encodes the Na-Cl co-transporter (NCCT). Gitelman syndrome is characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria, and renin-angiotensin-aldosterone system (RAAS) activation. Different *SLC12A3* variants may lead to phenotypic variability and severity.

Methods: In this study, we reported the clinical features and genetic analysis of a Chinese pedigree diagnosed with Gitelman syndrome.

Results: The proband exhibited hypokalaemia, hypomagnesemia, metabolic alkalosis, but hypercalciuria and kidney stone formation. The increased urinary calcium excretion made it confused to Bartter syndrome. The persistent renal potassium wasting resulted in renal tubular lesions, and might affect urinary calcium reabsorption and excretion. Genetic analysis revealed mutations of *SLC12A3* gene with c.433C > T (p.Arg145Cys), c.1077C > G (p.Asn359Lys), and c.1666C > T (p.Pro556Ser). Potential alterations of structure and function of NCCT protein due to those genetic variations of *SLC12A3* are predicted. Interestingly, one sibling of the proband carried the same mutant sites and exhibited similar clinical features with milder phenotypes of hypokalemia and hypomagnesemia, but hypocalciuria rather than hypercalciuria. Family members with at least one wild type copy of *SLC12A3* had normal biochemistry. With administration of spironolactone, potassium chloride and magnesium supplement, the serum

Endocrine CONNECTIONS

L Jiang, X Peng *et al.* | Structure and function of *SLC12A3* mutation | 11:1 | e210262

RESEARCH

Frequent *SLC12A3* mutations in Chinese Gitelman syndrome patients: structure and function disorder

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*(L Jiang and X Peng contributed equally to this work)

Abstract

Purposes: This study was conducted to identify the frequent mutations from reported Chinese Gitelman syndrome (GS) patients, to predict the three-dimensional structure

Key Words

- Gitelman syndrome

Case Report

ENDOCRINE SOCIETY

OXFORD

The Bartter-Gitelman Spectrum: 50-Year Follow-up With Revision of Diagnosis After Whole-Genome Sequencing

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Abstract

Bartter syndrome (BS) and Gitelman syndrome (GS) are renal tubular disorders affecting sodium, potassium, and chloride reabsorption. Clinical features include muscle cramps and weakness, in association with hypokalemia, hypochloremic metabolic alkalosis, and hyperreninemic hyperaldosteronism. Hypomagnesemia and hypocalciuria are typical of GS, while juxtaglomerular hyperplasia is characteristic of BS. GS is due to *SLC12A3* variants, whereas BS is due to variants in *SLC12A1*, *KCNJ1*, *CLCNKA*, *CLCNKB*, *BSND*, *MAGED2*, or *CASR*. We had the opportunity to follow up one of the first reported cases of a salt-wasting tubulopathy, who based on clinical features was diagnosed with GS. The patient had presented at age 10 years with tetany precipitated by vomiting or diarrhea. She had hypokalemia, a hypochloremic metabolic alkalosis, hyponatremia, mild hypercalcemia, and normomagnesemia, and subsequently developed hypocalciuria and hypomagnesemia. A renal biopsy showed no evidence for juxtaglomerular hyperplasia. She developed chronic kidney failure at age 55 years, and ocular sclerochoroidal calcification, associated with BS and GS, at older than 65 years. Our aim was therefore to establish the genetic diagnosis in this patient using whole-genome sequencing (WGS). Leukocyte DNA was used for WGS analysis, and this revealed a homozygous c.226C > T (p.Arg76Ter) nonsense *CLCNKB* mutation, thereby establishing a diagnosis of BS type-3. WGS also identified 2 greater than 5-Mb regions of homozygosity that suggested likely mutational heterozygosity in her parents, who originated from a Greek island with fewer than 1500 inhabitants and may therefore have shared a common ancestor. Our results demonstrate the utility of WGS in establishing the correct diagnosis in renal tubular disorders


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