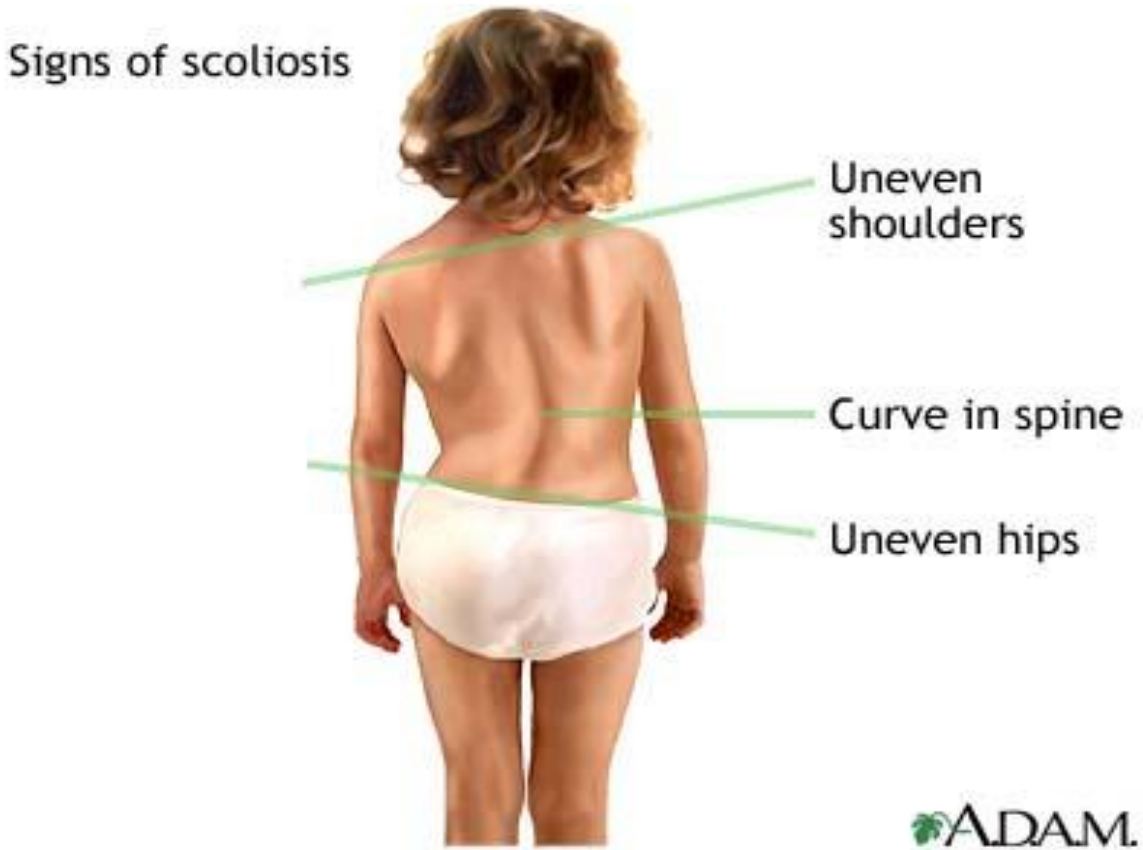
TUBULOPATHY

Intensive Care Unit

Sina Hospital

- A 13 years old female who is known case of Scoliosis.
- She was operated 2 months ago for spinal curve repair.
- PMH:EMG-MCV In 2 years old =>No Motoneuron Disease

  EMG-NCV 1391 Myopathy


Signs of scoliosis
Uneven shoulders
Curve in spine
Uneven hips
A.D.A.M.

- The patient was referred to E.R due to Dyspnea.
- She became gradually confused with a PaCO2=95 and then was Intubated in E.R , and transferred to ICU on 27.4.92

Patient Status at ICU

- At first was on assisted ventilation with SIMV mode
- Consciousness got better increasingly to full awake
- Ventilation was changed to Spont. mode with least support but patient remained intubated due to permanent high $PaCO_2$

PATIENT STATUS AT ICU

- **Hemodynamic**

MAP	57-93 31.4 4.5
CVP	8-15 (13) 2.5
Temp.	36.2 - 37.7 1.5(9pm) 28.4(12mn) 3.5(3pm)

- **Fluid balance**

Date	27.4	28.4	29.4	30.4	31.4	1.5	2.5	3.5	4.5
Intake	2840	2800	2855	2420	4100	3330	3350	3560	2820
Output	840	2700	3650	3570	2900	2400	3800	2450	2300

PATIENT STATUS AT ICU(LABS)

- The least Hb. was $\overset{7.4}{\underset{28.4}{}}$ => P/C 150cc transfused
- BS:80-110

123	127
27.4	27.4

- Na: $\overset{3}{\underset{28.4}{}}$ NaCl 5% drip => 135-138
- K: => 4.1-5
- Cr: <0.7

- Urea: 5-22
- Ca: 8.2-9.3
- Ph: 4-5.3
- Cl: 93 
- Liver enzyme: Normal range

PATIENT STATUS AT ICU (MEDICATION)

- Aminophyline 5mg/H (from 29.4)
- Digoxin 0.125mg /iv/Loading=> Main. 2days once (from 29.4)
- Acetazolamide 125mg + N/S 200-300cc 30 min thereafter (totally 5 dose from 2.5 to 5.5)
- Spironolacton (from 29.4)
- Vancomycine 500mg bid
- Cefepim 1gr bid
- Ranitidin
- Heparin
- Methadon

Patient Status (ABGs serial)

	27.4 ICU							28.4		29.4		30.4	
PH	7.36	7.37	7.26	7.19	7.23	7.36	7.45	7.41	7.33	7.28	7.33	7.42	7.42
PCO2	59	58	87	95	87	48	44	46	54	57	45	42	49
PO2	49	57	24	52	38	51	202	214	56	41	44	25	188
HCO3	33.3	33.5	39	36.3	36.4	27.1	30.6	29.2	28.5	26.8	23.7	27.2	31.8
BE	7.9	8.2	9.2	5.7	6.9	1.7	6.6	4.6	2.6	0.1	-2.2	2.7	7.3
SO2	83	88	33	77	60	84	100	100	86	69	76	47	100

PATIENT STATUS (ABGS SERIAL)

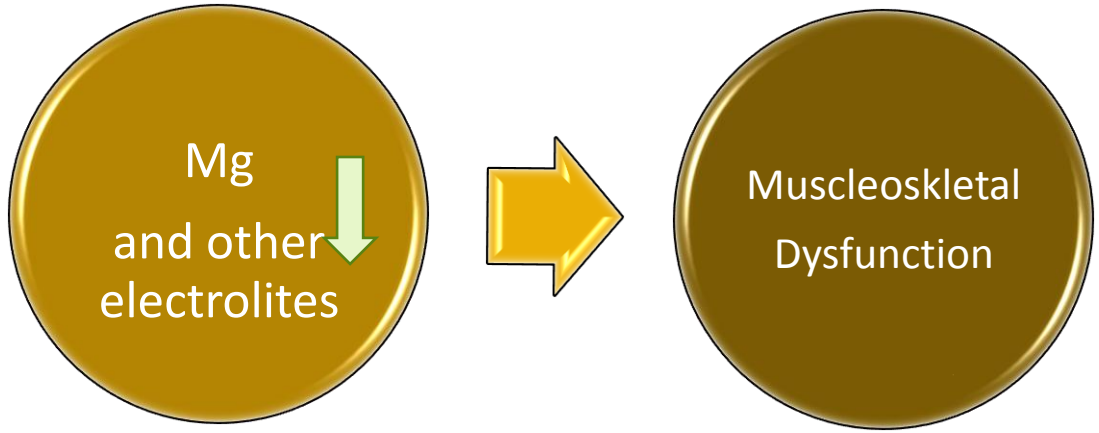
	31.4		1.5	2.5			3.5			4.5		5.5		6.5		
PH	7.53	7.41	7.41	7.3	7.32	7.3	7.31	7.25		7.27	7.33	7.35	7.31	7.31	7.31	7.29
PCO2	41	55	50	73	63	63	57	71		67	58	53	64	67	60	54
PO2	194	161	170	51	48	43	138	41		53	138	55	46	44	173	80
HCO3	34.3	34.9	31.7	35.9	32.5	31	28.7	31.1		30.8	30.6	29.3	32.2	33.7	30.2	26
BE	11.6	10.3	7.1	9.5	6.4	4.6	2.4	3.9		3.9	4.7	3.7	5.9	7.4	3.9	-0.6
SO2	100	99	100	82	80	73	99	67		82	99	87	77	75	99	94
				Aceta.	Aceta.		Aceta.			Aceta.		Aceta.		Aceta.		

- Na: 137.5
- Cl: 92
- HCO3 : 33 - 38
- Pco2 : 90
- pH: 7.3

- Respiratory Acidosis

- SID:
- Na – Cl > 40 -42 : Metabolic Alkalosis
- 137.5 – 92= 45.5

- Cl, Mg, Ph, Ca wasting



What do you think about…

TUBULOPHATY

TUBULOPATHY

- Bartter syndrome and Gitelman syndrome (also called tubular hypomagnesemia-hypokalemia with hypocalciuria)
- **autosomal recessive** disorders
- metabolic abnormalities

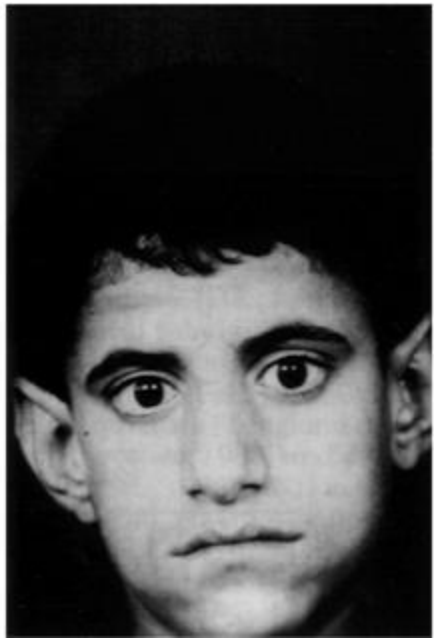
CLASSIFICATION

The inherited salt-losing renal tubulopathies

Disorder	Gene affected	Gene product	Clinical presentation	Functional studies
Bartter syndrome type I	SLC12A1	NKCC2	Antenatal Bartter syndrome (Hyperprostaglandin E syndrome)	Concentrating capacity reduced and diluting capacity reduced
Bartter syndrome type II	KCNJ1	ROMK	Antenatal Bartter syndrome	Concentrating capacity reduced and diluting capacity reduced
Bartter syndrome type III	CLCKB	CLC-Kb	Classical Bartter syndrome	Concentrating capacity reduced and diluting capacity reduced
Bartter syndrome type IV	BSND	Barttin (B-subunit of CLC-Ka and CLC-Kb)	Antenatal Bartter syndrome (Hyperprostaglandin E syndrome) and sensorineural deafness*	Concentrating capacity reduced and diluting capacity reduced
Bartter syndrome type IVB	CLCNKA and CLCNKB	CLC-Ka and CLC-Kb	Antenatal Bartter syndrome (Hyperprostaglandin E syndrome) and sensorineural deafness*	Concentrating capacity reduced and diluting capacity reduced
Bartter syndrome type V•	CaSR gene	CaSR	Bartter syndrome with hypocalcemia	Concentrating capacity reduced and diluting capacity reduced
Gitelman syndrome	SLC12A3	NCCT	Gitelman syndrome	Concentrating capacity normal/near normal and diluting capacity reduced

Genetics and presentation of Bartter and Gitelman syndromes. There are six Bartter syndrome subtypes (I, II, III, IV, IVB, and V) corresponding to six genetic defects.
NKCC2: furosemide-sensitive sodium-potassium-2 chloride cotransporter; ROMK: renal outer medullary potassium channel; CLC-Kb: chloride channel Kb; CLC-Ka: chloride channel Ka; CaSR: calcium sensing receptor; NCCT: thiazide-sensitive sodium-chloride cotransporter.
* Sensorineural deafness occurs because ClC-Ka and CLC-Kb are highly expressed in the inner ear and interact with other transport proteins (eg, NKCC1) to maintain the high potassium concentration in the endolymph that is required for normal hearing.
• Some experts classify the mild salt-losing effect of gain-of-function mutations in the calcium-sensing receptor as Bartter syndrome type V.

- Bartter syndrome is a rare metabolic renal tubular disorder characterized by :
  - Hypokalaemic
  - hypochloraemic metabolic alkalosis
  - normal blood pressure
  - hyper-reninaemia
  - increased urinary loss of sodium, potassium and chloride
- Its estimated prevalence is 1 per million



GITELMAN SYNDROME

- Children or young adults
- Mutation of genes encoding the human sodium chloride cotransporters and magnesium channels in the thiazide-sensitive segments of the distal convoluted tubule
- Gitelman syndrome prevalence is 1 in 40,000

- Impaired sodium chloride reabsorption leads to mild volume depletion and activation of the renin-angiotensin-aldosterone system

- The combination of secondary hyperaldosteronism and increased distal flow and sodium delivery enhances potassium and hydrogen secretion at the secretory sites in the connecting tubules and collecting tubules, leading to hypokalemia and metabolic alkalosis

- Patients with Bartter syndrome tend to have a blunted response to a loop diuretic, while patients with Gitelman syndrome tend to have a blunted response to a thiazide diuretic
- Urinary calcium excretion is normal or high in patients with Bartter syndrome, as it is with a loop diuretic, since calcium reabsorption in the thick ascending limb requires normal NaCl reabsorption. In contrast, urinary calcium excretion is typically reduced in patients with Gitelman syndrome as it is with a thiazide diuretic.

BARTTER'S SYNDROME

Clinical manifestation

- Growth and mental retardation
- Hypokalemia
- Metabolic alkalosis
- Polyuria and polydipsia due to decreased urinary concentrating ability
- Normal to increased urinary calcium excretion
- Normal or mildly decreased serum magnesium concentration
- Hypophosphatemia in occasional patients, with secondary hyperparathyroidism being a possible mechanism

Bartter-like phenotype with Aminoglycosides

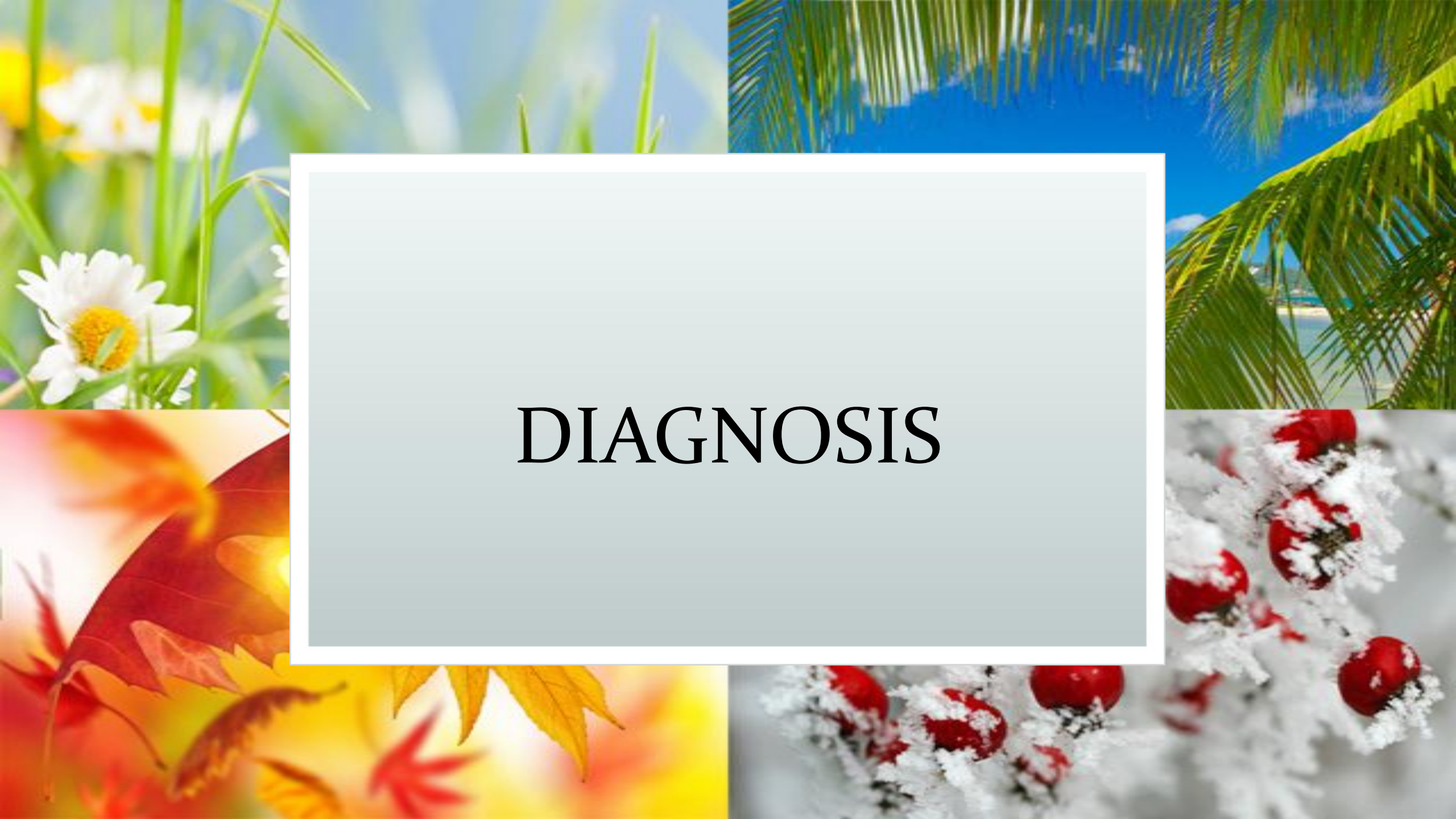
- hypokalemia, metabolic alkalosis, hypomagnesemia with urinary magnesium wasting, and hypercalciuria
- resolve two to six weeks after drug termination
- polycations, which act as calcimimetics and can activate the calcium-sensing receptor (CaSR)

GITELMAN SYNDROME

- Cramps of the arms and legs, which may be severe, are observed in almost all patients. They are due at least in part to hypokalemia and hypomagnesemia; the latter is due both to renal magnesium wasting and reduced intestinal magnesium absorption . Approximately 10 percent of affected patients have tetany at diagnosis.
- Fatigue, which may be severe. This is more common in those with greater degrees of renal salt wasting, leading to reduced blood pressure
- Polyuria and nocturia are found in approximately 50 and 80 percent of patients, respectively. The polyuria is probably due

- to salt and water loss. The underlying genetic defect should not affect concentrating ability because function in the medullary thick ascending limb is relatively intact. However, chronic hypokalemia is a cause of nephrogenic diabetes insipidus
- Chondrocalcinosis (calcium pyrophosphate deposits and arthritis) may occur and may be related to chronic severe hypomagnesemia
- Rarely, patients present at a young age and have growth retardation

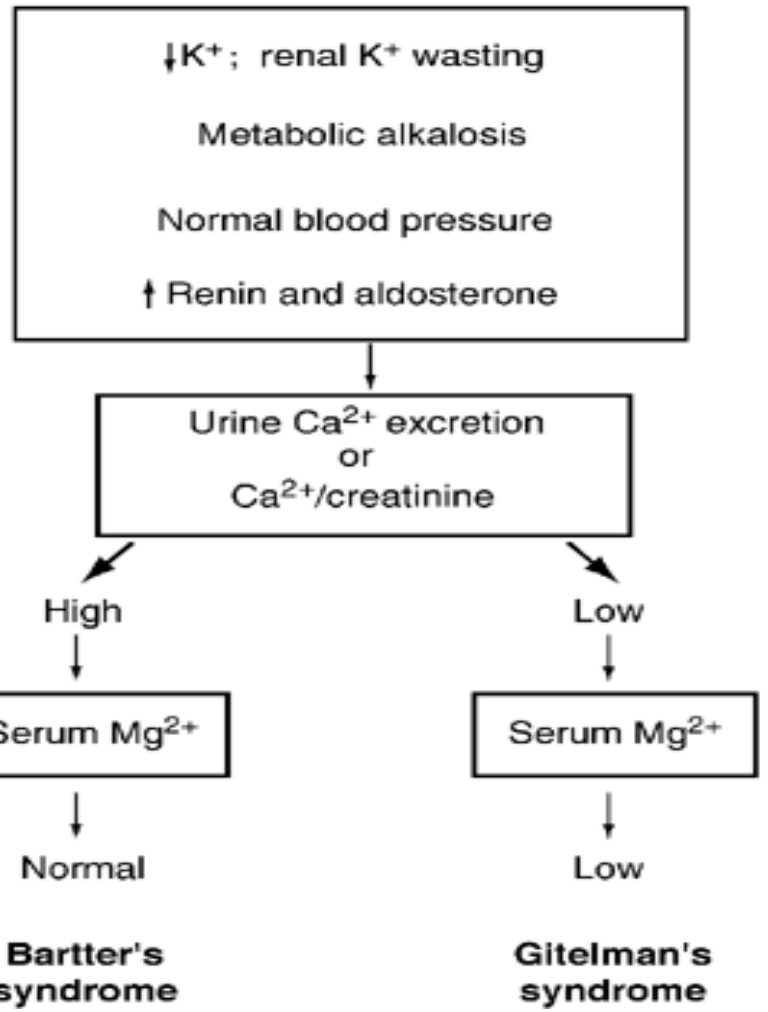
- Surprisingly, hypertension may develop later in life. In a series of 36 patients with Gitelman syndrome from 35 unrelated families, nearly half (44 percent) developed hypertension later in life (median 55 years), many despite treatment with potassium-sparing diuretics. The reason for this observation is not known, but it may relate to prolonged exposure to elevated renin and aldosterone levels
- Some but not all series have found more severe potassium wasting in females corresponding to an increased need for potassium and magnesium replacement during pregnancy. The apparently more severe phenotype in women may be related to the effects of female sex hormones on the expression or function of the Na-Cl cotransporter



DIAGNOSIS

- The diagnosis is usually made with a careful history, physical examination, measurement of the urine chloride concentration, and a urine diuretic screen.

- Other tests, such as genetic testing and measurement of the change in fractional excretion of chloride in response to loop and thiazide diuretics, are not widely performed


↓K+; renal K+ wasting
Metabolic alkalosis
Normal blood pressure
↑ Renin and aldosterone
Urine Ca2+ excretion
or
Ca2+/creatinine
High
Low
Serum Mg2+
Serum Mg2+
Normal
Low
Bartter's syndrome
Gitelman's syndrome

DIFFRENITIAL DIAGNOSIS

- Surreptitious vomiting
- Surreptitious diuretic use
- Cystic fibrosis : lose salt-rich sweat during hot summer months
- Infants given chloride deficient liquid formula can develop hypokalemia and metabolic alkalosis
- Nephrotoxic agents such as Cisplatin chemotherapy
- tubulointerstitial nephritis in the setting of Sjögren syndrome : electrolyte abnormalities resembling Gitelman syndrome

- These conditions have sometimes been called "pseudo-Bartter syndrome" or "pseudo-Gitelman syndrome," terms that have also been applied to self-induced vomiting and surreptitious diuretic use.

RESPONSE TO THIAZIDE AND LOOP DIURETICS

- The tubular defects in sodium chloride transport are almost identical to that seen with chronic ingestion of a loop diuretic (mimicking Bartter syndrome) or a thiazide diuretic (mimicking Gitelman syndrome)

- One study formally tested the response to oral Hydrochlorthiazide (50 mg in adults or, in children or adolescents, 1 mg/kg) among 41 patients with genetically confirmed Gitelman syndrome, seven patients with genetically confirmed Bartter syndrome, and four patients with either surreptitious vomiting or diuretic use . A blunted thiazide response (defined as less than a 2.3 percent increase in the fractional excretion of chloride) was found in 38 of the 41 patients with Gitelman syndrome and in none of the patients with Bartter syndrome, surreptitious vomiting or diuretic use. The formula for the fractional excretion of chloride is similar to that for the fractional excretion of sodium, which is mostly used in the evaluation of acute kidney injury (acute renal failure).

ROLE OF PROSTAGLANDINS

impaired entry of sodium chloride into the macula densa cells at the end of the thick ascending limb of the loop of Henle

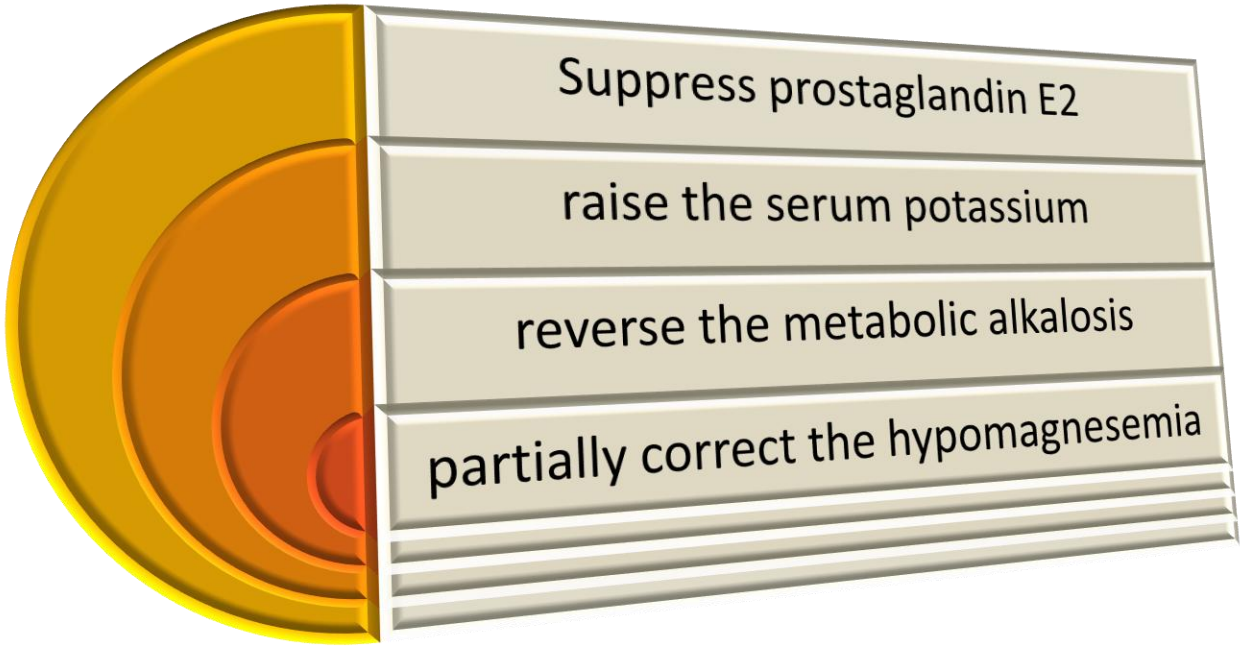
increases the expression of cyclooxygenase 2

Renal prostaglandin E2 (PGE2) production is often markedly elevated in the types of Bartter syndrome characterized by severe symptoms and presentation in utero or in the neonate (type I, II, IV and IVB)

TREATMENT

NSAIDs and potassium-sparing diuretics

- The preferred initial therapy



ANGIOTENSIN INHIBITORS

- useful adjunctive therapy

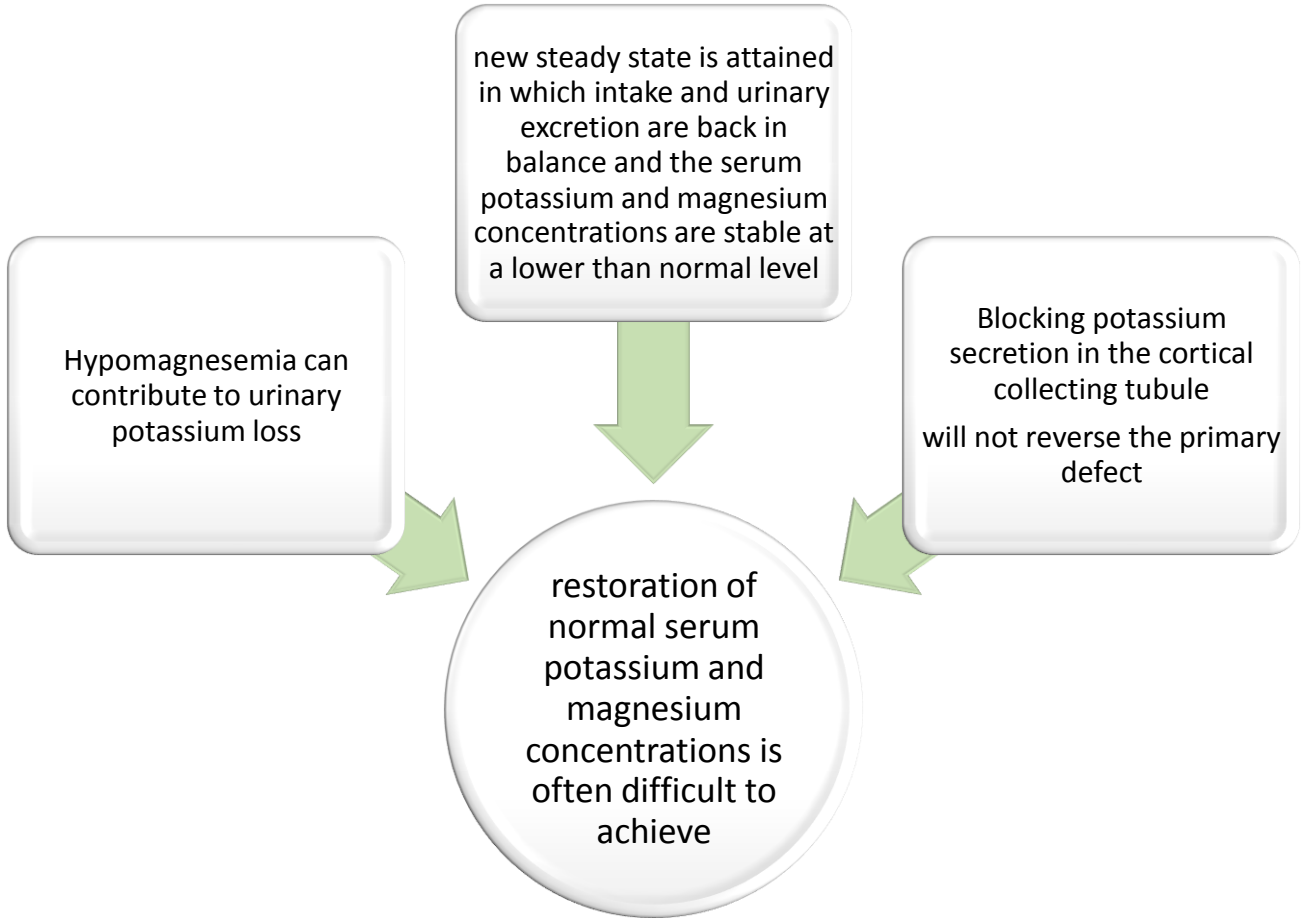
- Enalapril : In a report of seven patients with Bartter syndrome, for example, the serum potassium rose from 2.4 to 3.9 meq/L after three months of therapy, there was also partial correction of hypomagnesemia

- Angiotensin receptor blockers (ARBs) should have similar efficacy but have not been well studied in these patients

- The acute reduction in circulating angiotensin II levels
- symptomatic hypotension
- transient and can be minimized by the initial use of low doses

POTASSIUM AND MAGNESIUM SUPPLEMENTATION

- NSAIDs and/or potassium-sparing diuretics is often incompletely effective



RENAL TRANSPLANTATION

- Renal transplantation should correct the transport abnormalities

- Ibuprofen
- Spirnolacton
- Losartan
- Hypertonic NaCl
- Mg up to 14g/day
- AND High Chloride Diet

CASE REPORTS

Clinical Case Report

An unusual cause of failure to thrive in a child

PURNIMA SAMAYAM, RAVI CHANDER B., SUDHA REDDY V. R.

His weight at the time of presentation to us was 9.17 kg, height 92 cm (both <3rd centile) and orbitofrontal cortex (OFC) measurement 48 cm. He was febrile with some dehydration and pallor, normal blood pressure, distended urinary bladder and depressed deep tendon jerks. Investigations showed that his haemoglobin was 10 g/dl, the total leukocyte count was 3400/cmm with 80 neutrophils, 18 lymphocytes and 2 eosinophils. His serum sodium was 117 mEq/L, potassium 2.2 mEq/L, urea 34 mg/dl and creatinine 0.4 mg/dl. With treatment, his vomiting subsided and hydration status improved; but the serum sodium was 126 mEq/L, chloride 85 mEq/L and potassium 2 mEq/L. This

Case Reports

A case of Bartter syndrome

R P S Rajapakshe[1], G M Bandaranayake[2], A P Wijesuriya[3]

Sri Lanka Journal of Child Health, 2010; **39**: 148-149

(Key words: Bartter syndrome, hypokalaemia, metabolic alkalosis, polyuria, indomethacin)

Introduction

Bartter syndrome is a rare, recessive, defect of sodium and chloride absorption from the loop of Henle resulting in excessive urinary electrolyte losses. Due to volume depletion, hyperaldosteronism leads to hypokalaemia and metabolic alkalosis.

Case Report

being normal (135meq/l), potassium (2.5meq/l) and chloride (92meq/l) were low. His arterial blood gas revealed metabolic alkalosis with a pH of 7.56 and serum and urinary osmolalities were 270mosm/kg water and 159mosm/kg water respectively. His urine electrolytes revealed increased excretion of sodium, potassium and chloride. Although normocalcaemic, his urinary calcium/creatinine excretion ratio was elevated (0.68), indicating hypercalciuria. His subsequent ultrasound scan of abdomen was normal.

EMHJ • Vol. 18 No. 12 • 2012

Eastern Mediterranean Health Journal
La Revue de Santé de la Méditerranée orientale

Case report

Bartter syndrome presenting as poor weight gain and dehydration in an infant

N.E.R. Alkhateeb[1] and Z.T. Gardee[1]

Case Report

Status epilepticus as the only presentation of the neonatal Bartter syndrome

Soumya Patra, Mithun C. Konar, Rajarshi Basu, Ajoy K. Khaowas[1], Soumyadeep Dutta[2], Debanjali Sarkar[3]

Departments of Pediatric Medicine, [1]Otorhinolaryngology and [2]Orthopedics, N.R.S Medical College and Hospital, Kolkata, [3]Department of Obstetrics and Gynecology, MGM Medical College, Kishanganj, Bihar, India

ABSTRACT

Bartter syndrome is a rare hereditary (autosomal recessive) salt-losing tubulopathy characterized by hypokalemia, hypochloremia, metabolic alkalosis, and normal blood pressure with hyperreninemia, The underlying renal abnormality results in excessive urinary losses of sodium, chloride, and potassium. We report a case of a four-month-old infant with neonatal Bartter syndrome, who presented only with status epilepticus. To the best of our present knowledge, there is no reported case of Bartter syndrome who presented with status epilepticus.

Key words: Bartter syndrome, neonate, status epilepticus

TANHKS FOR YOUR PATIENCE