APCN x TSN 2025
23rd Asian Pacific Congress of Nephrology
Gene, Immunology, Vast, MEtabolism at its Finest!

APSN-TSN CME(1)

An Overview

Bartter & Gitelman Syndrome

CAROLINE ENG

PAEDIATRIC NEPHROLOGIST

TUANKU JA'AFAR HOSPITAL, SEREMBAN

MALAYSIA

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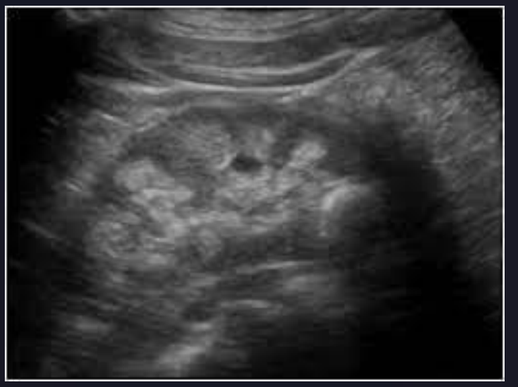
#Case Vignette One

A 3-year-old girl, TKZ

- Referred for evaluation of **failure to thrive**.
- Been smaller than her peers and had a poor appetite.
- Mother thought she urinates frequently (polyuria), often soaking through her diapers.
- History of maternal polyhydramnios during the third trimester of pregnancy, although the child was born at term.

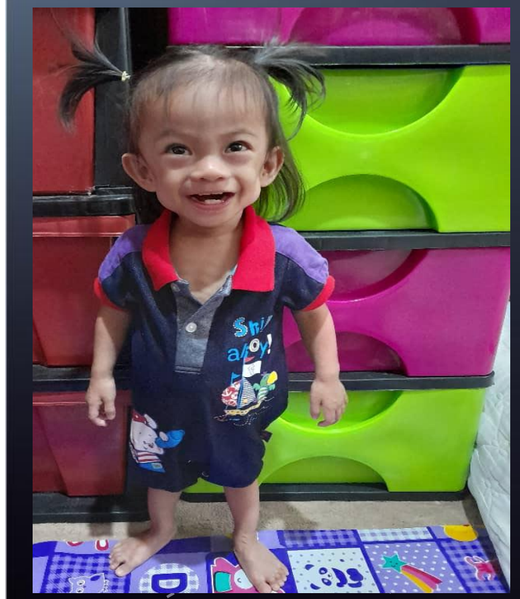
•**Vitals:** Blood pressure was in the **normal** range for age (95/60 mmHg).
•**Growth:** Weight and height were **below the 3rd percentile for her age.**
•**General:** thin with signs of mild dehydration, including dry mucous membranes and decreased skin turgor.
•**Head and Neck:** No dysmorphic facial features are noted.
•**Cardiovascular/Respiratory/Abdominal Exams:** Unremarkable.

Sodium (Na+). 132 mEq/L	Bicarbonate (HCO3-). 30 mEq/L
Potassium (K+)2.5 mEq/L	Serum Magnesium. 0.5mmol/L
Chloride (Cl-)88 mEq/L	Corrected Calcium. 2.30 mmol/L



WES analysis: homozygous loss-of-function mutation in the ***CLCNKB* gene**, which encodes the ClC-Kb chloride channel

#Case Vignette Two



At 2 (taken with permission)

Ex-prematurity at 27 weeks (Birth weight 1.5kg) with a maternal history of polyhydramnios. Had a brief episode of Neonatal AKI, which was attributed to fluid restriction for a concurrent patent ductus arteriosus, and creatinine upon discharge declined from a peak of 160 to 50s umol/L.

- Lost from follow-up; she presented again with failure to thrive (4.3kg at 1 year) and subtle facial dysmorphism (triangular face, frontal bossing and small chin)
- She had polyuria (up to 8ml/kg/hr) and polydipsia
- Pressures normotensive
- Initial investigations showed electrolyte abnormalities: metabolic alkalosis with hypokalemia (K~ 2.2-2.8) and hypernatremia (Na ~ 150-155) to which she remained asymptomatic.
- Creatinine 50 umol/L
- Corrected Calcium borderline low 1.8-2.0
- Urine Calcium Creatinine ratio 2.06 mg/mg
- High urine chloride FeCL >0.5%
- USG Kidney showed early nephrocalcinosis

❖ Serum Renin & aldosterone were elevated

❖ Whole exome sequencing:

Gene	Variant	Classification	Disease
SLC12A1	15-48543951-GA-G NM_000338.3:c.1927del (NP_000329.2:p.Thr643LeufsTer7) Homozygous	Likely pathogenic	Bartter syndrome, type 1

Positive A likely pathogenic variant was identified.

THE AMERICAN JOURNAL of MEDICINE
Official Journal of the Alliance for Academic Internal Medicine

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CLINICAL STUDY · Volume 33, Issue 6, P811-828, December 1962

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Hyperplasia of the juxtaglomerular complex with hyperaldosteronism and hypokalemic alkalosis

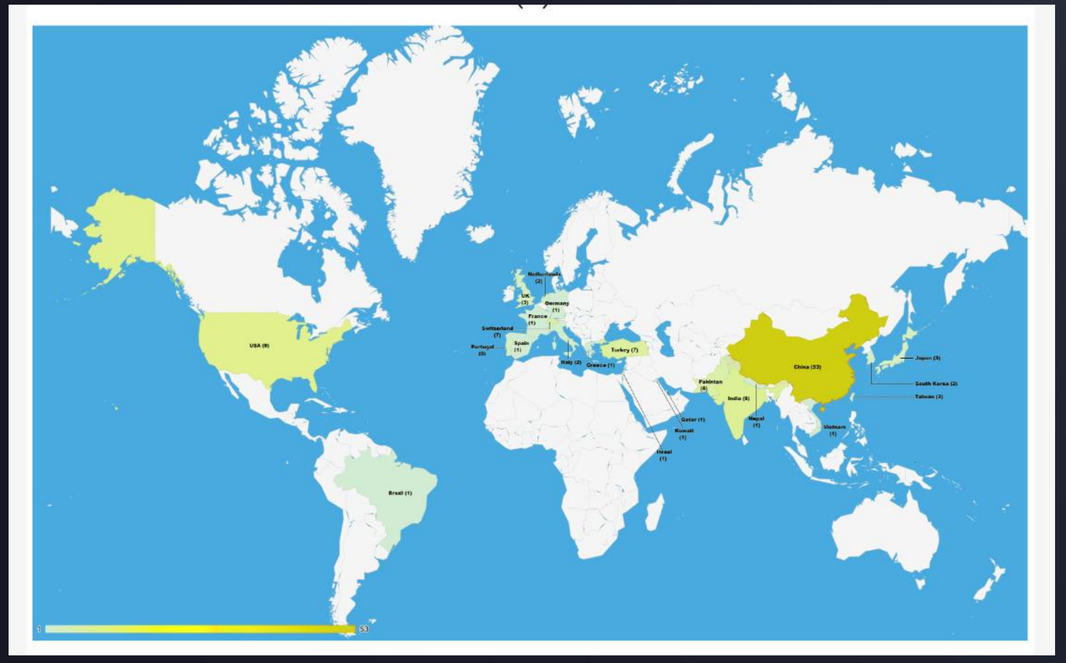
A new syndrome

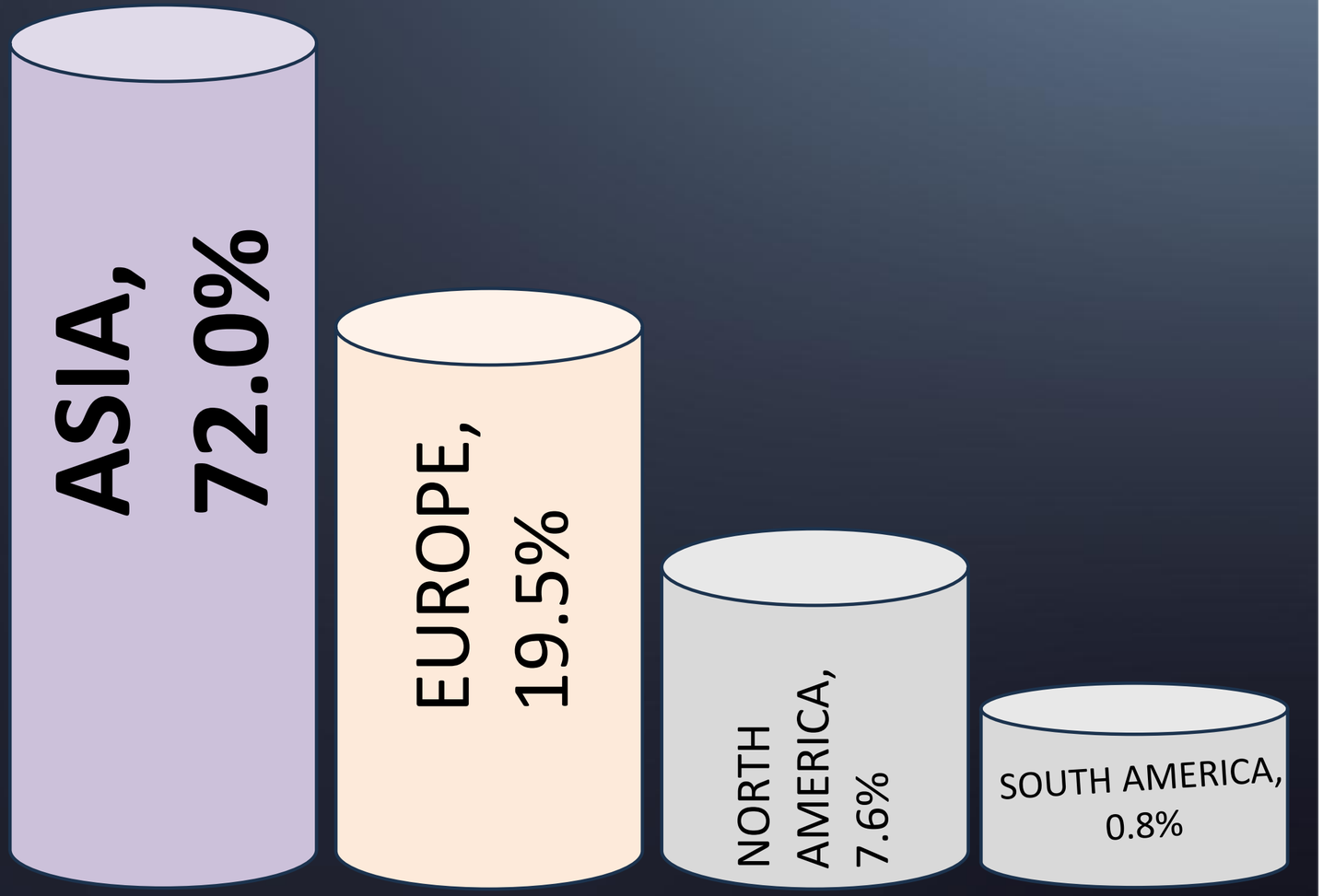
Frederic C. Bartter, M.D. · Pacita Pronove, M.D. · John R. Gill, Jr., M.D. · Ross C. MacCardle, Ph.D.

- Dr Frederic Bartter and his colleagues in 1962
- in a seminal paper in the December issue of the American Journal of

Bartter Syndrome Overview

1 IN 1,000,000 -1,200,000 PEOPLE (more uncommon than GS)





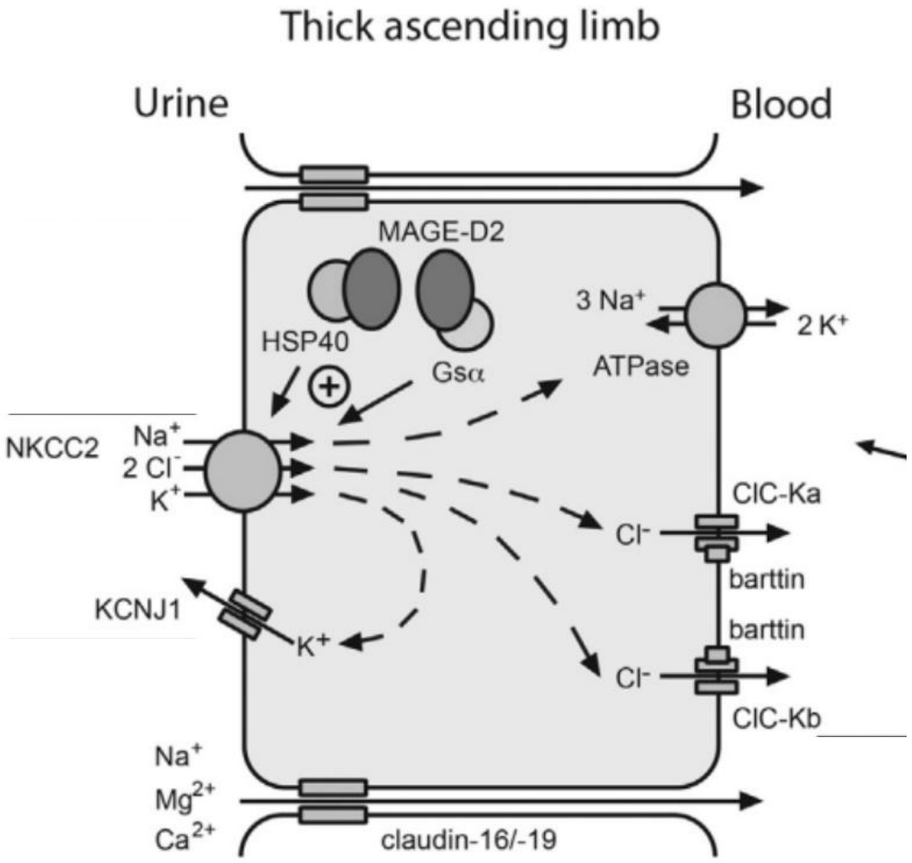
Qasba, R. K., net al
Bartter Syndrome: A Systematic Review of Case Reports and Case Series. *Medicina*, *59*(9), 1638.

Review > Pediatr Int. 2020 Apr;62(4):428-437. doi: 10.1111/ped.14089. Epub 2020 Apr 13.

Inherited salt-losing tubulopathy: An old condition but a new category of tubulopathy

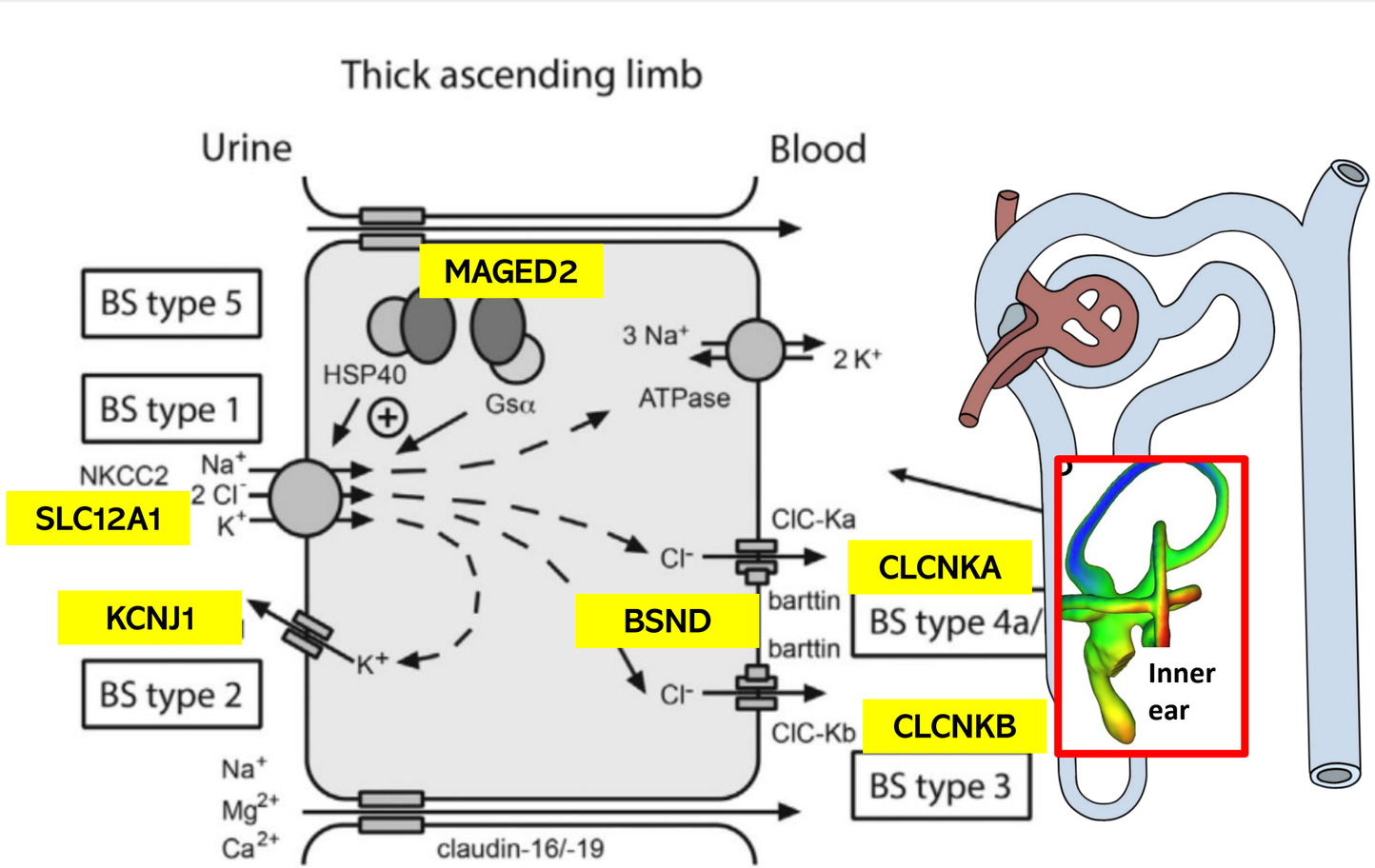
Kandai Nozu [1], Tomohiko Yamamura [1], Tomoko Horinouchi [1], China Nagano [1], Nana Sakakibara [1], Kenji Ishikura [2], Riku Hamada [3], Naoya Morisada [1], Kazumoto Iijima [1]

Bartter syndrome (BS) and Gitelman syndrome (GS) are syndromes associated with congenital tubular dysfunction, characterized by hypokalemia and metabolic alkalosis. Clinically, BS is classified into two types: the severe antenatal/neonatal type, which develops during the fetal period with polyhydramnios and preterm delivery; and the relatively mild classic type, which is usually found during infancy with failure to thrive. GS can be clinically differentiated from BS by its age at onset, usually after school age, or laboratory findings of hypomagnesemia and hypocalciuria. Recent advances in molecular biology have shown that these diseases can be genetically classified into type 1 to 5 BS and GS. As a result, it has become clear that the clinical classification of antenatal/neonatal BS, classic BS, and GS does not always correspond to the clinical symptoms associated with the genotypes in a one-to-one manner; and there is clinically no clear differential border between type 3 BS and GS. This has caused confusion among clinicians in the diagnosis of



NKCC is a luminal channel responsible for reabsorption of sodium along with chloride and potassium

- NKCC: key transporter at the TAL Loop of Henle to reabsorb sodium, potassium, and chloride ions from the tubular lumen
- ROMK - recycles potassium
- Basolateral side: Na+-K+-ATPase pump maintains the sodium gradient
- Basolateral chloride channels from the ClC family enable chloride exit
- Mg and Cal reabsorption – down the electrochemical gradient



M Konrad et al.: Diagnosis and management of Bartter syndrome

Across the board, **any form of genetic mutation** ultimately …

DEFECTIVE NaCl TRANSPORT AT TAL

REDUCE voltage driven PARACELLULAR REABSORPTION OF CA2+

ELEVATED CALCIUM EXCRETION IN URINE

HYPERCALCIURIA/ NEPHROCALCINOSIS

INCREASED DELIVERY OF NACL TO DISTAL NEPHRON

VOLUME CONTRACTION

RAAS ACTIVATION → HIGH RENIN/SECONDARY HYPERALDOSTERONISM & JGA HYPERPLASIA

NA REABSROPTION AT DISTAL IN EXCHANGE WITH H+/K+

HYPOK / METABOLIC ALKALOSIS

INCREASED PRODUCTION OF PGE2

POTENT VASODILATOR

BLUNTED VASCULAR RESPONSE TO ANGIOTENSIN II

Normal BP

INCREASED BONE REABSORPTION

HIGH URINARY PROSTAGLANDIN

POLYURIA

IMPAIRED VASOPRESIN STIMULATED URINARY CONCENTRATION

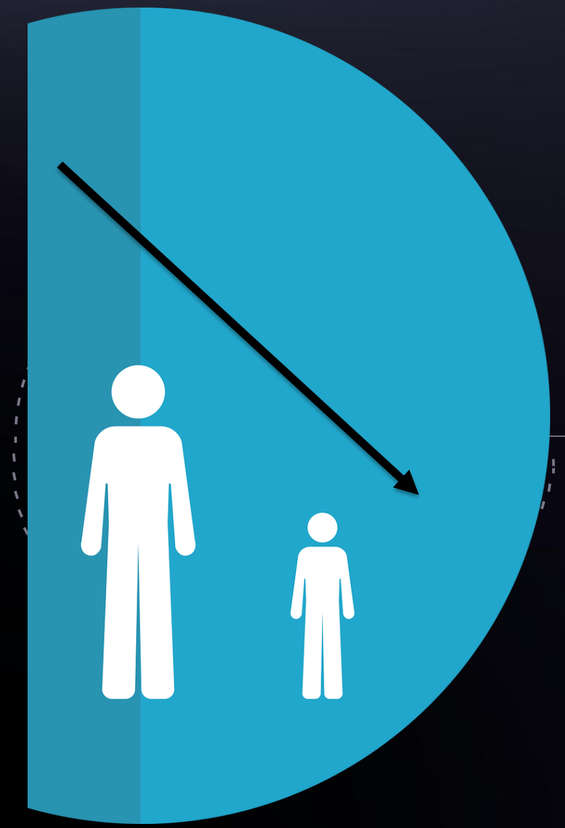
Clinical Presentation of Bartter Syndrome

CHARACTERISTICS	TYPE 1	TYPE 2	TYPE 3	TYPE 4	TYPE 5
Gene	SLC12A1	KCNJ1	CLCNKB	BSND CLCNKA / B	MAGED2
Inheritance	AR	AR	AR	AR	XLR
Age onset	Prenatal	Prenatal	0-5yr / “Classical”	Prenatal	Prenatal
Polyhydramnios	Severe	Severe	Mild / Absent	Severe	Severe
Clinical features	**Polyuria, hypochloremia, Hypokalemia, metabolic alkalosis, Failure to thrive**				
Hypokalemia	+	+	+++	+++	+
Hypercalciuria	++	++	+/-	+/-	+
Nephrocalcinosis	Very Frequent			Rare / mild	
Others			Mild hypoMagnesemia	Sensorineural hearing loss	Transient disease; resolves by term
	High risk of progressing to ESKD			Most severe form, HIGHER RISK OF progressing to ESKD	

#Case Vignette Three

A 14 year old boy AR

- Admitted for trauma. Incidentally picked up to have metabolic alkalosis with abnormal electrolytes.
- BP in the ward was noted to be low normal.



Sodium (Na+). 125 mEq/L	Blood pH 7.48. Bicarbonate (HCO3-). 30 mEq/L
Potassium (K+) 2.4 mEq/L	Serum Magnesium. 0.4mmol/L
Chloride (Cl-) 94 mEq/L	Corrected Calcium. 2.1 mmol/L

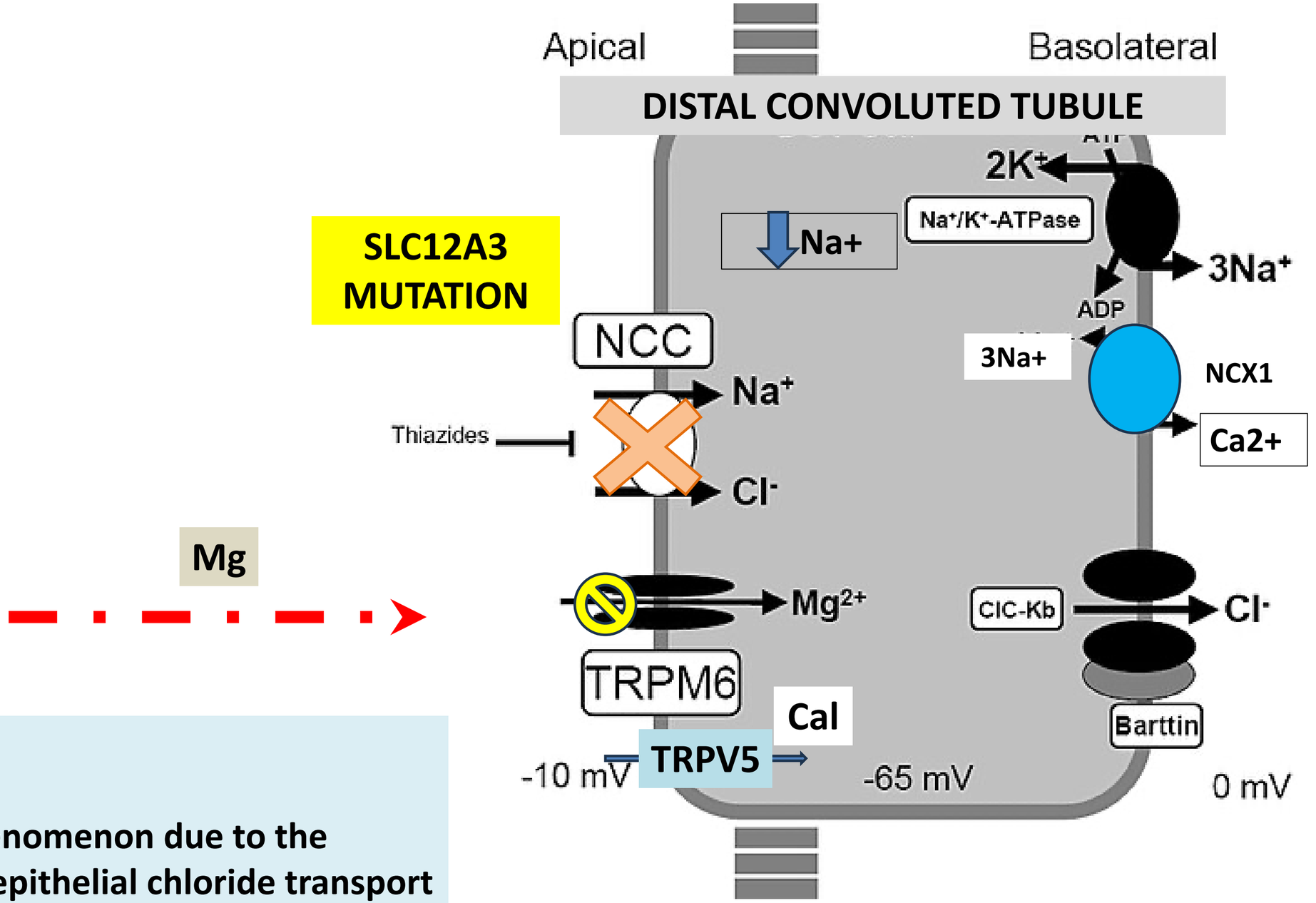
Subsequent investigation : HYPOCALCIURIA
USG Kidney: Normal study

Gitelman Syndrome Overview

In 1966, Dr Hiller Gitelman (*University of North Carolina School of Medicine)* and his colleagues first identified and described this inherited kidney condition.

- 1 to 10 in 40,000;
- with higher prevalence in Asia
- **Most of the time, this is fortuitously diagnosed**

❖**Mild features**
❖**Occurring late in Adolescence/ adulthood**
❖**Severe phenotype < 6 years old has been described**



❖A phenomenon due to the Transepithelial chloride transport defect in the DCT

Clinical features in GS

Defect at NCC → increased delivery of Na to distal nephron

Volume contraction

Heightened absorption of NA in exchange of K+ /H+

HIGH RENIN with SECONDARY HYPERALDOSTERONISM

- HYPOKALEMIC METABOLIC ALKALOSIS

Intensified Calcium absorption

- HYPOCALCIURIA
- ABSENCE OF NEPHROCALCINOSIS

Reduced Magnesium absorption

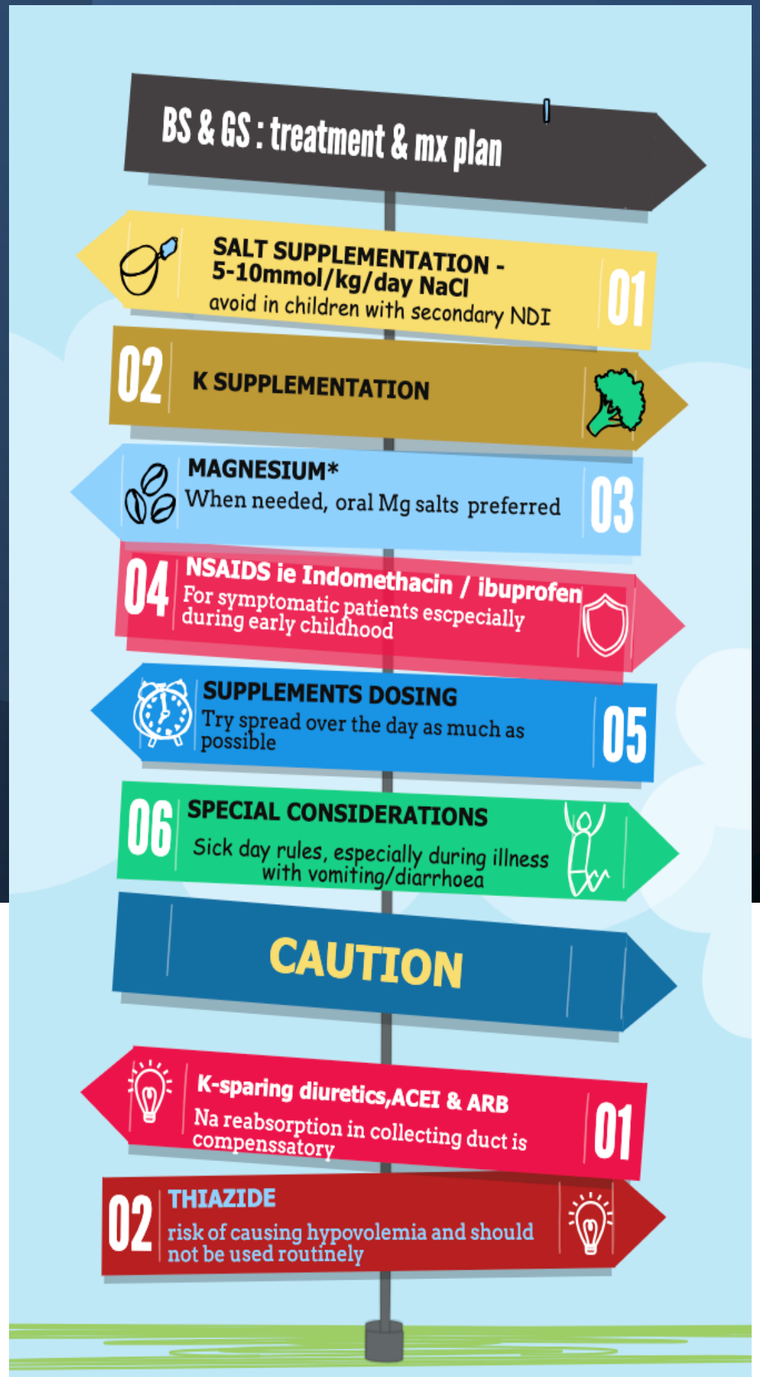
- HYPOMAGNESEMIA
- CHONDROCALCINOSIS / SCLEROCHOROIDAL CALCIFICATIONS

MANAGEMENT PLANNING ~ BS / GS

IMPORTANT TO MAINTAIN HOMEOSTASIS

- Infants and young children – every 3-6 months
  - Depending on severity
  - To ensure **adequate metabolic control**
  - Growth and psychomotor development

- Older children- established therapy and stable, every 6-12 months



executive summary www.kidney-international.org

Diagnosis and management of Bartter syndrome: executive summary of the consensus and recommendations from the European Rare Kidney Disease Reference Network Working Group for Tubular Disorders

Check for updates

OPEN

Gitelman syndrome: consensus and guidance from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

CrossMark

OPEN

Anne Blanchard[1,2,3,4], Detlef Bockenhauer[5,6], Davide Bolignano[7], Lorenzo A. Calò[8], Etienne Cosyns[9], Olivier Devuyst[10], David H. Ellison[11], Fiona E. Karet Frankl[12,13], Nine V.A.M. Knoers[14], Martin Konrad[15], Shih-Hua Lin[16,17] and Rosa Vargas-Poussou[2,18]

BARTTER SYNDROME

****Salt craving and high spontaneous salt intake is typical for individual with BS.**
NA supp: usually needed especially in younger children. *CAUTION when patient has secondary DI – risk of hyperNa dehydration.*

K: Potassium chloride supplements administered in water or in a slow-release formulation. The dose will be titrated according to an individual balance. **Target >3.0**

MG: *May be needed in BS Type 3*

NSAIDS: helpful to improve electrolyte profile and growth parameters.
Tapering or cessation may be possible in stable patients. Caution with chronic use and use during pregnancy.

K SPARING/ACEI &ARB: ? used in difficult-to-treat symptomatic hypokalemia with caution to avoid hypotension.
Caution: drugs may worsen renal sodium wasting/risk of symptomatic hypovolemia

THIAZIDE : ? to reduce hypercalciuria (no data on efficacy in BS). Not routine, to be used with caution

GITELMAN SYNDROME

Encourage patients to follow their propensity for salt consumption.

MG: Vital to correct this first in GS as Mg repletion facilitates K repletion.
Organic salts (e.g.aspartate, citrate, lactate) offer higher bioavailability. **Target >0.6**

NSAIDS: Indomethacin are rarely used in GS, because urinary prostaglandin E2 levels in GS are usually normal.

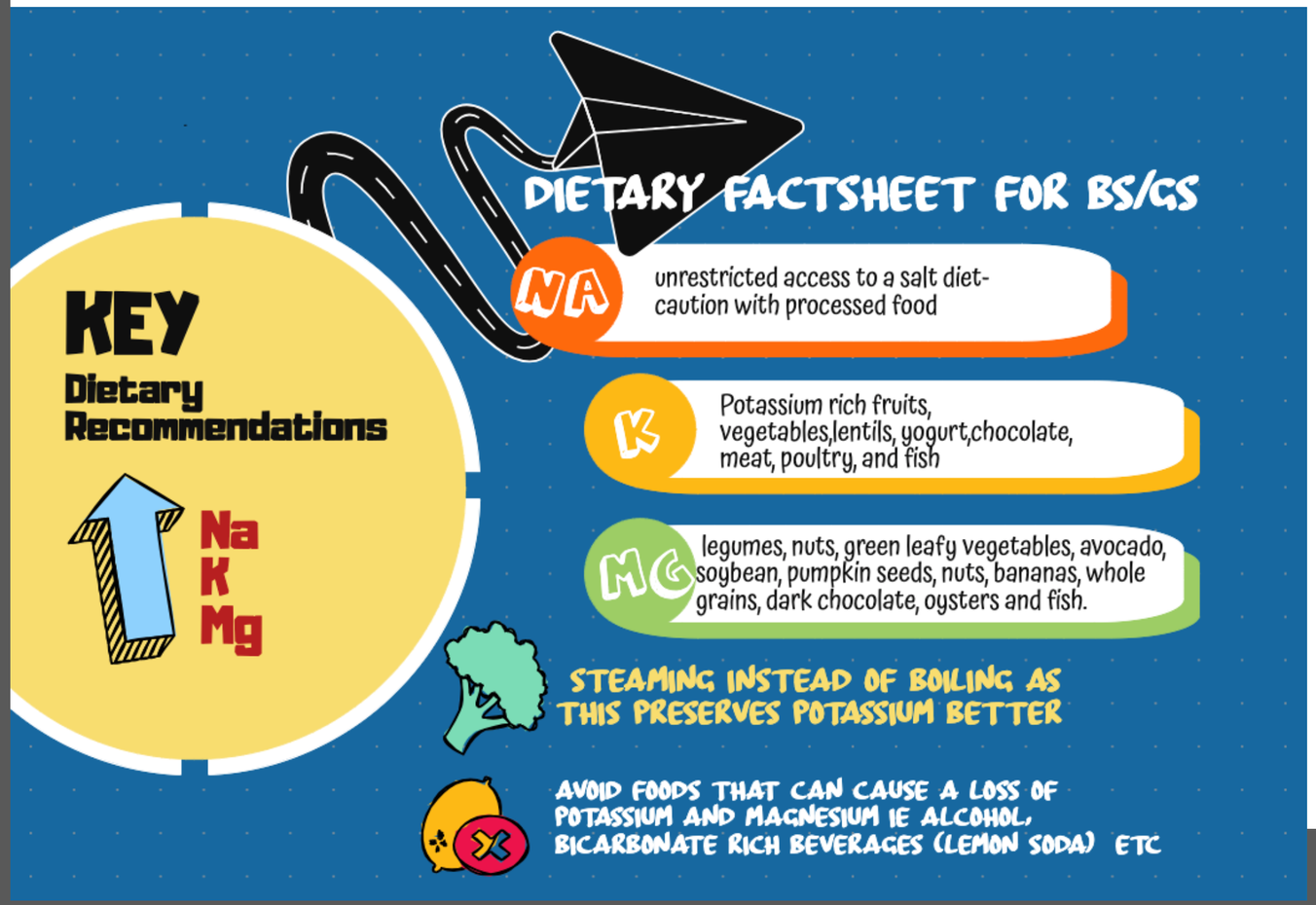
Review > Nutrients. 2021 Aug 26;13(9):2960. doi: 10.3390/nu13092960.

The Dietary Approach to the Treatment of the Rare Genetic Tubulopathies Gitelman's and Bartter's Syndromes

Francesco Francini [1], Laura Gobbi [2], Verdiana Ravarotto [2], Silvia Toniazzo [1], Federico Nalesso [2], Paolo Spinella [1], Lorenzo A Calò [2]

Affiliations + expand

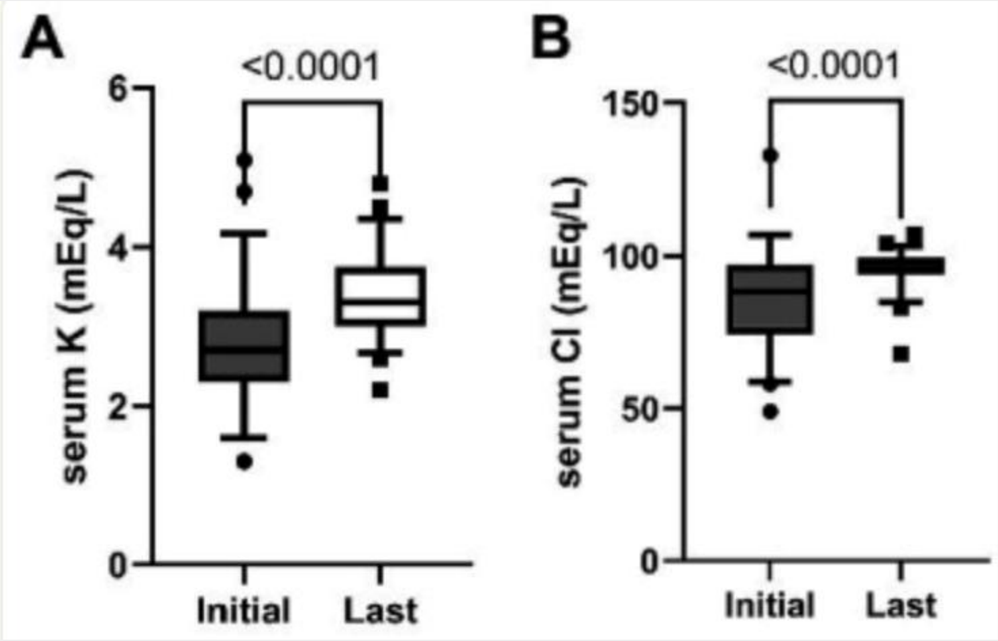
PMID: 34578838 PMCID: PMC8467039 DOI: 10.3390/nu13092960



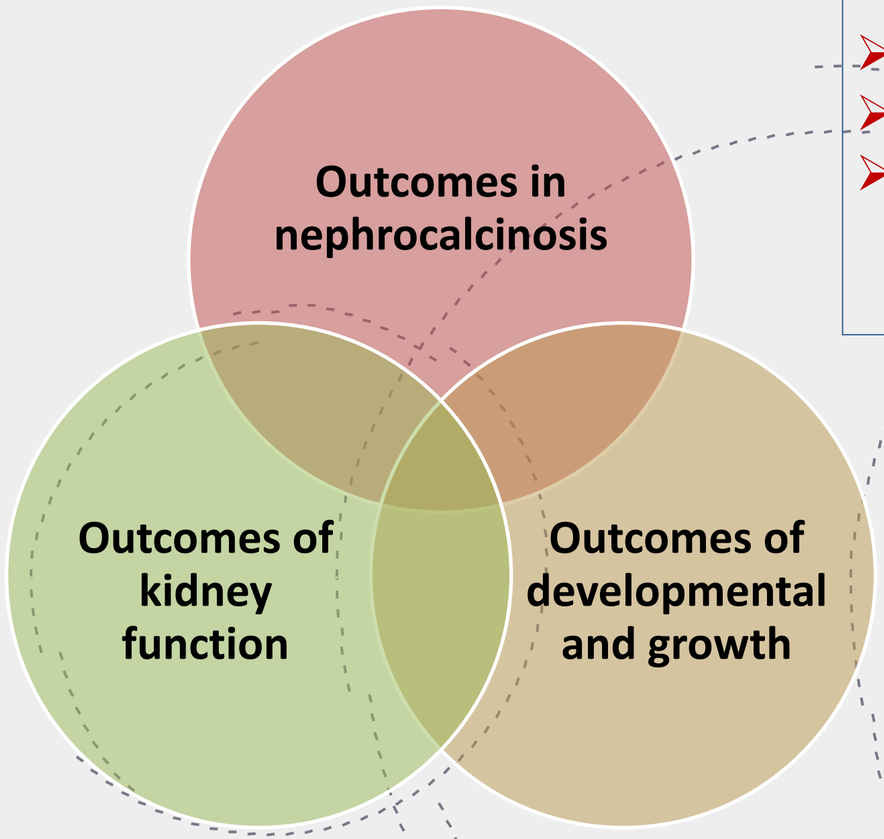
- A dietary approach to BS and GS complements medical therapy through modifying the consumption of sodium, potassium, and magnesium-rich foods and/or supplements containing these minerals.
- A nutritional consultation should be made available
- Would allow individuals and families to live better with the disease

Long-term outcome of Bartter syndrome in 54 patients: A multicenter study in Korea

Choi N, Kim SH, Bae EH, Yang EM, Lee KH, Lee SH, Lee JH, Ahn YH, Cheong HI, Kang HG, Hyun HS, Kim JH. Front Med (Lausanne). 2023 Mar 13;10:1099840.



BS patients require a large amount of potassium supplementation along with potassium-sparing agents throughout their lives, ***but tend to improve with age.***



- Observed in 35% of cohort
- 100% in BS 1 / 2
- 12.5% in BS3
- Disappearance of Nephrocalcinosis in 4 patients

- 41% remained short (height <3rd percentile) at the last visit
- Noteworthy, 3 patients from this cohort had GH

- 6 out of 54 (11%) of the patients developed at least CKD 3 – with a median age in the 3rd decade in the CKD group
- Only one had nephrocalcinosis

Clinical Characteristics, Symptoms and Long-term Outcomes in Gitelman Syndrome

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods and cohort

Electronic survey through ERKNet*

N = 587 (13 countries, 148 pediatric)

61% males in pediatric subgroup, 60% females in adult subgroup

Genetic test in 93% with SLC12A3 variants in 94% (73% compound heterozygous, 27% homozygous)

*Physician survey Jan - Aug 2024; Patient survey using Patient-Reported Outcomes Measurement Information System/PROMIS (Netherlands, Oct 24 – Jan 25

Findings

Growth & Body weight
Children are shorter & lighter (To general population)
Lower body weight persisted into adulthood [Weight – 2SD in 11%]

Laboratory values
Blood potassium, magnesium, sodium, chloride, and phosphate were lower than in the general population, while blood calcium and bicarbonate were higher

Long-term outcome
Adults had lower rates of CKD and HTN, but a higher rate of albuminuria or proteinuria than the general population

Reported symptoms
Fatigue, muscle cramps & salt craving in children (20-24%) & adults (25-60%)
Lower blood potassium & magnesium correlates with higher symptom score

Extrarenal features: Adults had a high prevalence of chondrocalcinosis (15%) and elevated blood cell counts (26%)

KI REPORTS

Wieërs MLAJ et al, 2025

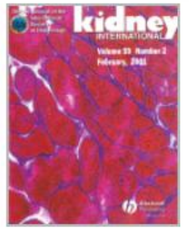
Visual abstract by:

Conclusion This study provides new insights into Gitelman Syndrome, highlights the disease burden and areas for future

Michiel L.A.J. Wieërs et al. Volume 10, Issue 11, November 2025, Pages 3967-3983

Quality of Life , QoL

Kidney International
Volume 59, Issue 2, February 2001, Pages 710-717



GS is not an asymptomatic disease

Clinical Nephrology – Epidemiology – Clinical Trials

Gitelman's syndrome revisited: An evaluation of symptoms and health-related quality of life

Dinna N. Cruz, Andrea J. Shaer, Margaret J. Bia, Richard P. Lifton, David B. Simon

50 adult GS patients with confirmed mutations

The most common symptoms were salt craving, with musculoskeletal symptoms such as cramps, muscle weakness, and aches and constitutional symptoms such as fatigue, generalized weakness and dizziness, and nocturia and polydipsia.

Significantly LOW QoL score from control

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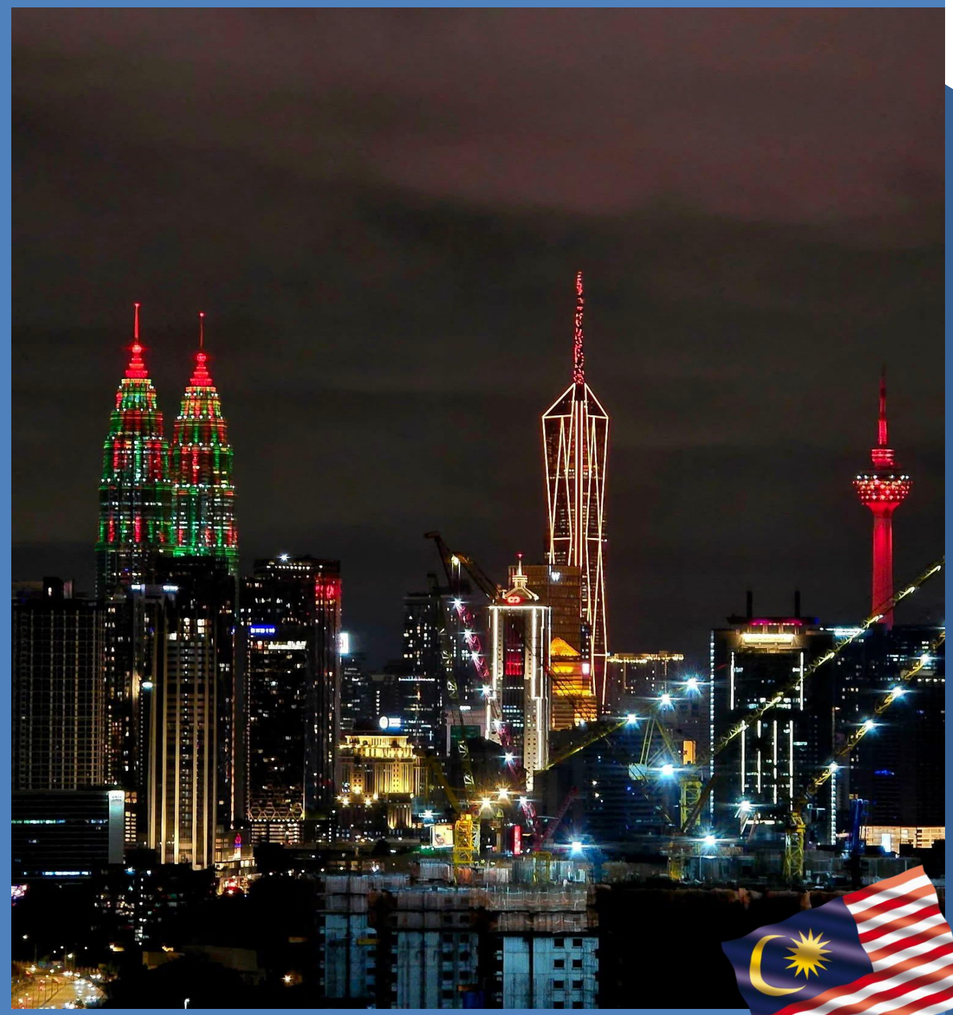

THANK YOU

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