Severe Asymptomatic Hypokalemia In A Family Cluster Of Gitelman Syndrome

The Apex Data Base: Apex Kidney Care, Sushrut Hospital and Research Centre.

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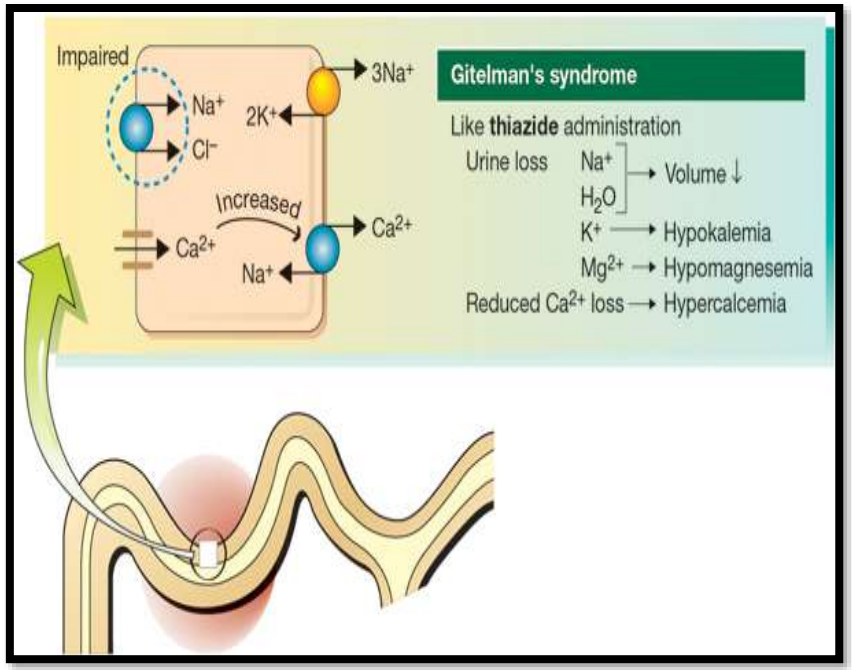
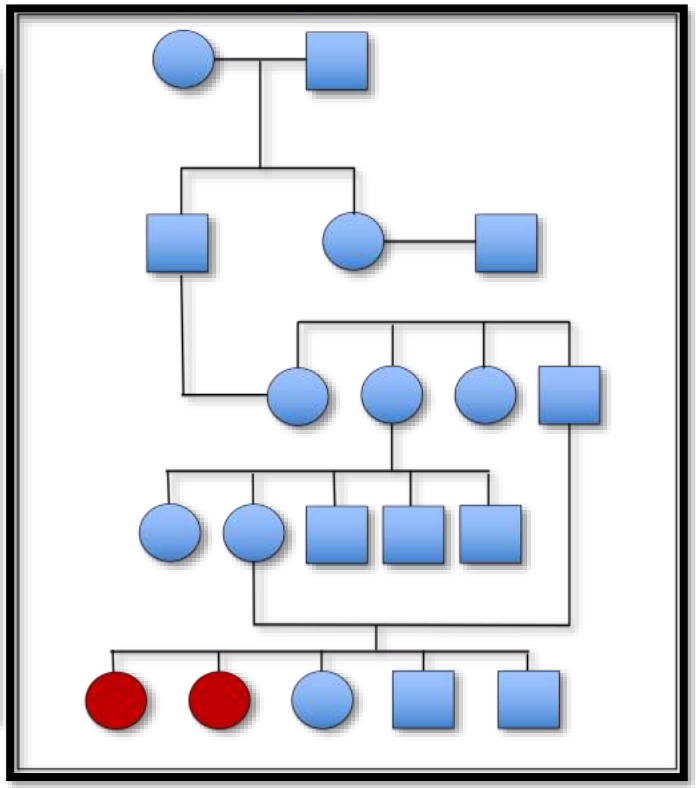
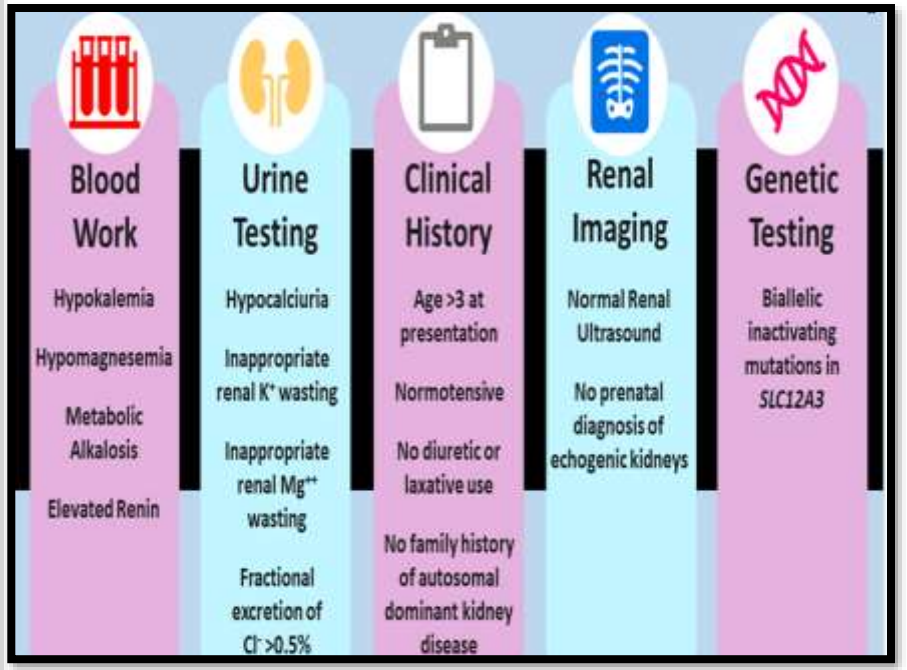


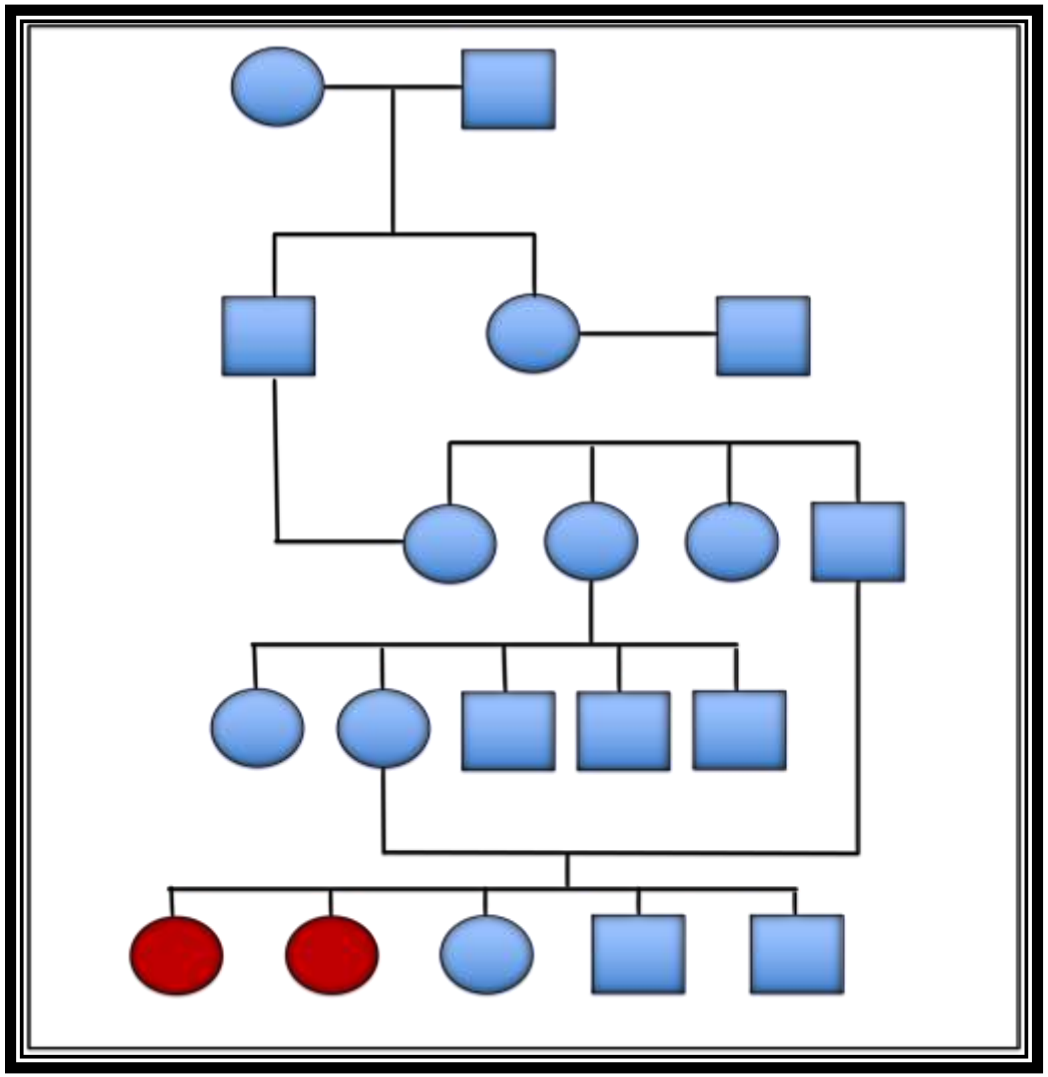




Case Report-Severe asymptomatic hypokalemia in a family cluster of Gitelman syndrome

Clinical Features

- Two sisters, aged 25 and 23 years, born out of a **consanguineous marriage** in 2 consecutive generations, were incidentally found to be **hypokalemic with serum potassium ranging between 1.4 to 2.1 mEq/L in both**, when being evaluated for menstrual irregularities.
- They were **normotensive** and had no other symptoms.
- Other than intermittent episodes of **generalized weakness** on enquiry, the **two sisters led a normal academic and professional life**.



Investigations

LAB PARAMETER	SISTER-1	SISTER-2
Serum Creatinine (mg/dl)	0.7	0.8
Serum Sodium(meq/l)	137	138
Serum Potassium (meq/l)	1.4	2.1
Serum Magnesium(meq/l)	2	2.2
Urine K/Creatinine Ratio(mmol/gm)	33	202
Urine Calcium/creatinine ratio	0.01	0.02
SLC12A3 variant (p. Ile840Ter) Homozygous state	Present	Present

Treatment

The mainstay of treatment included:

- High salt diet
- Oral potassium- (maximum 100meq/day-in severe cases did not exceed 3meq/kg/day)
- Magnesium supplements.

Conclusion

- Classically, GS has been considered as a **benign variant** of salt-losing nephropathies, with most cases being diagnosed during **adolescence or adulthood in routine evaluation, often asymptomatic or mild.**

- Here we present **2 cases of severe asymptomatic hypokalemia** which is attributable to **compensatory or adaptive** response by the body over years.

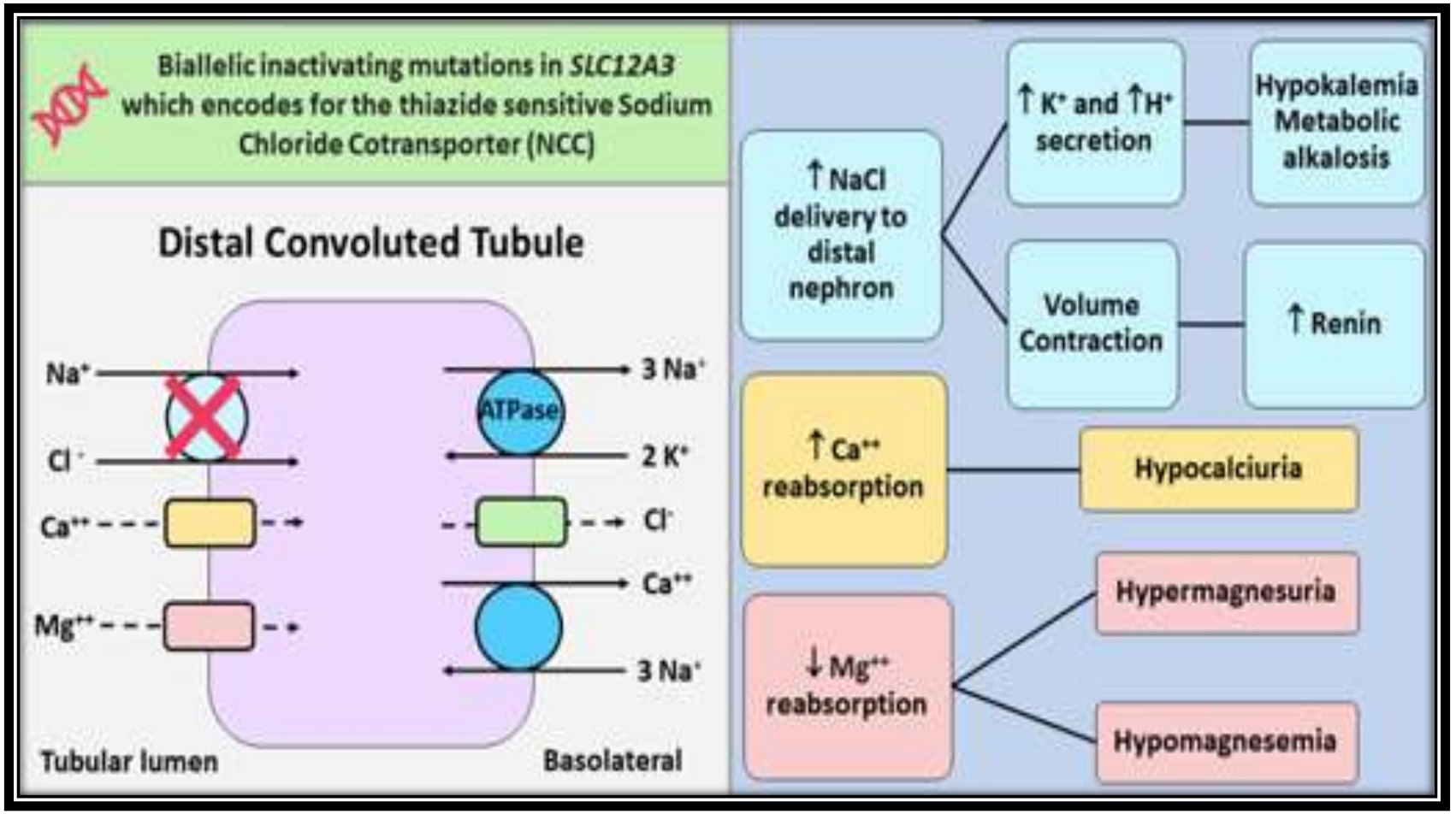
- The **genetic analysis helped confirm the diagnosis as well as supported marriage counselling for both the girls to avoid consanguinity**.

Discussion

Genetic mutations in Hypokalemia

	Disease	Inheritance	Cell/organ	OMIM	Mutated gene	Channels/proteins
Increased K^+ shift	FPP, type I/II	AD	Skeletal muscle	170400	*CACNA1S/SCN4A*	Dihydropyridin-sensitive voltage gated Ca^{2+} channel/ tetrodotoxin-sensitive Na^+ channel
	Andersen's syndrome	AD	Skeletal muscle, heart	600681	*KCNJ2*	Kir2.1 channel
Gastrointestinal K^+ loss	CLD	AR	Colon, ileum	214700	*DRA*	$Cl^-/OH^-(HCO_3^-)$ exchanger
Sweat K^+ loss	CF	AR	Sweat gland	602421	*CFTR*	Chloride channel
Renal K^+ loss with MES	GRA	AD	Adrenal glands	103900	*Chimeric CYP11B1/CYP11B2*	11β-hydroxylase/aldosterone synthase
	CAH	AR	Adrenal glands	202010/202110	*CYP11B1/CYP17*	11β-hydroxylase/17α-hydroxylase
	Liddle's syndrome	AD	CD, kidney	177200	*SCNN1B/SCNN1G*	β or γ subunit of epithelial Na^+ channel
	AME	AR	CD, kidney	207765	*HSD11B2*	11β-hydroxysteroid dehydrogenase type 2
Renal K^+ loss with normotension and metabolic alkalosis	BS, type I	AR	LOH	601678	*SLC12A1*	$Na^+/K^+/2Cl^-$ cotransporter
	BS, type II	AR	LOH	241200	*KCNJ1*	ROMK channel
	BS, type III	AR	LOH, DCT	607364	*CLCNKB*	Kidney-specific basolateral Cl^- channel
	BS, type IV	AR	LOH/inner ear	602522	*BSND*	Barttin
	BS, type V	AR	LOH/parathyroid	601199	*CASR*	Calcium-sensing receptor
	GS	AR	DCT	263800	*SLC12A3*	Thiazide-sensitive Na^+/Cl^- cotransporter
	SeSAME syndrome	AR	DCT/brain/inner ear	612780	*KCNJ10*	Kir4.1 channel
Renal K^++ loss with normotension and metabolic acidosis	pRTA with ocular lesion	AR	PCT, eye	604278	*SLC4A4*	Basolateral Na^+/HCO_3^- cotransporter
	dRTA with deafness	AR	CD, inner ear	267300	*ATP6V1B1/ ATP6V0A4*	Apical H^+-ATPase of α-intercalated cells
	dRTA with/without anemia	AR	CD, RBC	602722	*SLC4A1*	Basolateral HCO_3^-/Cl^-exchanger
	Combined pRTA and dRTA	AR	PCT, CD, bone	259730	*CAII*	Carbonic anhydrase II

Gitelman syndrome-Pathophysiology and Biochemical Abnormalities

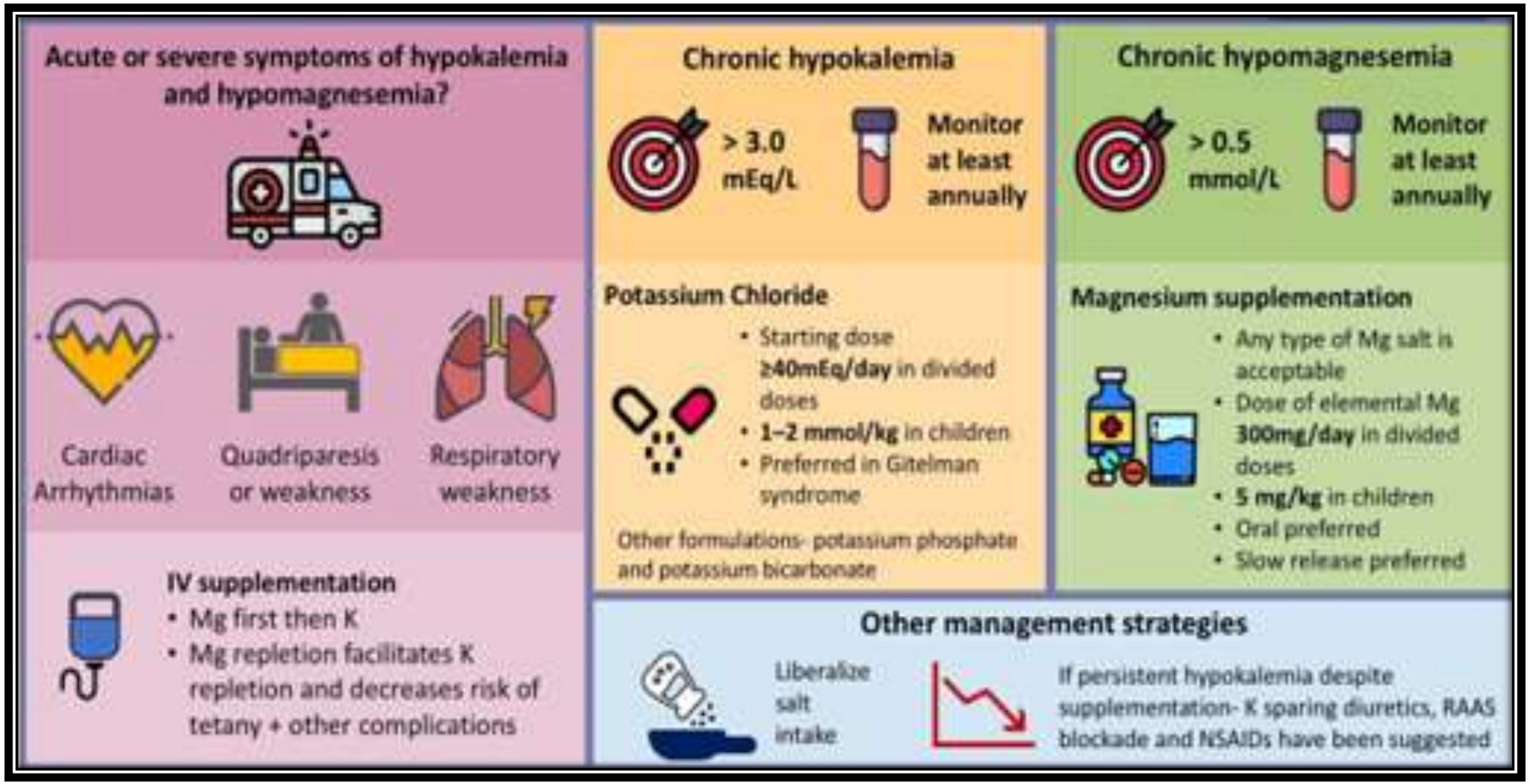


Clinical features of Gitelman syndrome

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

- **The severity of the clinical presentation in hypokalemia depends on the degree and duration of low serum K+ levels.**
- **Our patients did not show myopathy or ECG changes despite severe hypokalemia which could be attributed to a compensatory or adaptive response by the body over years and hence asymptomatic and presenting with laboratory abnormalities alone**

Management of Gitelman syndrome



About the Mutation

- **More than 100 mutations(SLC12A3 gene)-mostly missense,.**
- **Nonsense, frameshift, and splice-site (ss) defects and gene rearrangements have also been described.**
- **Benign variant of salt-losing nephropathies.**
- **Presentation- adolescence or adulthood , mild or asymptomatic**
- **Diagnosis-routine evaluation**
- **Considerable phenotypic variability-pts with different mutations, same mutation in unrelated patients and those of same family**
- **Molecular basis of phenotypic variability is unknown**
- **Genetic background and environmental effects-influence disease severity**

Thank you