



Gitelman Syndrome: What the Clinician Needs to know

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Abstract

Gitelman syndrome has a prevalence of 1-10/40,000, representing the most common inherited disease of renal tubules. It is due to inactivating mutations of the SLC12A3 gene that encodes the thiazide-sensitive Sodium Chloride Cotransporter (NCC) located in the apical membrane of the distal convoluted tubules, resulting in hypokalemic metabolic alkalosis associated with hypomagnesemia and hypocalciuria. Although it is generally considered a benign tubular disease, a number of complications have been observed in some patients. Increased sodium intake along with a diet rich in potassium and magnesium is essential, but a number of patients requires intravenous potassium or magnesium infusion. In certain patients, amiloride, spironolactone, eplerenone, or renin angiotensin system blockers can be administered.

Keywords

Gitelman syndrome, Potassium, Hypokalemia, Metabolic alkalosis, Hypomagnesemia, Hypocalciuria

Gitelman syndrome is the most common autosomal recessive inherited disease of renal tubules with a prevalence of 1-10/40,000. It is characterized by hypokalemic metabolic alkalosis associated with hypomagnesemia and hypocalciuria [1-4]. The disease is due to inactivating mutations of the SLC12A3 gene that encodes the thiazide-sensitive Sodium Chloride Cotransporter (NCC) located in the apical membrane of the distal convoluted tubules [5-7]. Less often, the condition results from mutations in the CLCNKB gene encoding the chloride channel ClC-Kb, the cause of classic Bartter syndrome [1]. The detection of biallelic inactivating SLC12A3 mutations (currently used methods have high sensitivity and specificity) is crucial for the diagnosis of Gitelman syndrome, but in patients who do not have two mutations in SLC12A3 the clinical sensitivity (proportion of positive tests if the disease is present) is 65% to 80%. Available next generation sequencing gene panels should at least include the SLC12A3, CLCNKB, and HNF1B genes [1]. Certain founder mutations are observed in populations such as European Gypsies and genetic testing can establish the diagnosis [8-10]. It should be mentioned that there is weak association between genotype and clinical phenotype in Gitelman syndrome.

Gitelman syndrome is usually detected during adolescence or adulthood in patients with symptoms re-

lated to the coexisting electrolyte abnormalities (Table 1) [1,11]. Most of these clinical findings are related to chronic hypokalemia and hypomagnesemia which can be identified in serum chemistry and can help in the diagnosis of the syndrome (Table 2) [1,12,13]. It should be mentioned that even though it was initially regarded as a benign tubular disease, a number of complications have been observed in some patients with Gitelman syndrome (Table 3) [1,14-23].

Gitelman syndrome should be differentiated from acquired causes of hypokalemic nonperiodic paralysis, tubulopathies due to diuretic abuse, bulimia nervosa or chronic vomiting, autoimmune disorders and drugs, from genetic disorders such as Bartter syndrome as well as diseases arisen from mutations in the KCNJ10 and HNF1 β genes (Table 4) [24-31].

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Table 1: Clinical and electrocardiographic manifestations in Gitelman syndrome.

- Muscle weakness-fatigue-dizziness
- Cramps-occasionally rhabdomyolysis
- Salt craving
- Nocturia-thirst-polydipsia
- Paresthesia- numbness
- Low blood pressure
- Carpopedal spasms-tetany
- Gastrointestinal symptoms (intestinal paresis, vomiting, constipation)
- In some patients arthritis due to chondrocalcinosis is observed
- In a few cases early onset of the disease associated with failure of thrive and growth retardation as in Bartter syndrome is found
- Ataxia
- Prolonged QT interval in the electrocardiogram-cardiac arrhythmias

Table 2: Usual laboratory findings in patients with Gitelman syndrome.

- Hypokalemia (serum K^+ < 3.5 mmol/L) associated with inappropriate kaliuresis (potassium/creatinine in a random urine specimen > 18 mmol/mg)
- Hypomagnesemia (serum magnesium < 0.7 mmol/L) associated with renal magnesium wasting (fractional magnesium excretion > 4%)
- Hypocalciuria (calcium/creatinine in a random urine specimen < 0.07 mg/mg)
- Metabolic alkalosis
- Increased chloride excretion (fractional chloride excretion > 0.5%)
- Hyperreninemia
- Hypophosphatemia (occasionally)
- Genetic diagnosis: Inactivating mutations in the SLC12A3 gene encoding the thiazide sensitive Sodium-Chloride Cotransporter (NCC)

Table 3: Complications in patients with Gitelman syndrome.

- Cardiac arrhythmias and prolonged QT interval due to coexistent hypokalemia and hypomagnesemia
- Chondrocalcinosis leading to pseudogout
- Sclerochoroidal calcifications
- Renal dysfunction (hypokalemic nephropathy or due to hyperreninemic hyperaldosteronism)
- Glucose intolerance due to coexistent hypokalemia/hypomagnesemia (rarely)
- Hypokalemic rhabdomyolysis (very rare)

Increased sodium intake along with a diet rich in potassium and magnesium is essential for patients' management. Additionally, oral potassium and magnesium supplementation is needed in most patients aiming at increasing serum potassium and magnesium levels (> 3 mmol/l and 0.6 mmol/l, respectively) [1,32-34]. The dose of these supplements should be carefully individualized to avoid their side effects. In severe electrolyte imbalanc-

Table 4: Differential diagnosis in patients with suspected Gitelman syndrome.

Genetic disorders

- Bartter syndrome: normal magnesium levels are commonly observed, other common findings include young age, failure to thrive, and polyuria
- Mutations in the KCNJ10 gene coding for the KCNJ10/Kir4 (an autosomal recessive disorder characterized by the EAST syndrome [epilepsy, ataxia, sensorineural deafness and tubulopathy])
- Mutations in HNF1 β gene coding for the transcription factor HNF1- β (dominant mode of inheritance). Other clinical manifestations are common (early renal disease, renal cysts, maternity onset diabetes mellitus, increased transaminases and urogenital malformations)

Acquired disorders

- Diuretics abuse: a urine screen for diuretics is useful
- Bulimia nervosa and chronic vomiting: urinary chloride levels are usually < 25 mEq/L
- Autoimmune disorders such as Sjogren's syndrome (appropriate tests are necessary)
- Drugs such as cisplatin: drug history is mandatory

Table 5: Treatment of Gitelman syndrome.

- Increased NaCl intake, diet rich in K^+ and Mg^{2+}
- Oral potassium supplementation (mainly KCl; > 40 mEq/d with meals; target: serum potassium > 3 mEq/L)
- In severe symptomatic cases intravenous KCl should be carefully administered in hypotonic saline solutions (< 50 mmol/L at a rate of < 10 ml/h)
- Oral magnesium supplementation (mainly organic salts, such as aspartate, citrate, lactate or $MgCl_2$; 300 mg/d (12.24 mmol/L) in 2-4 doses (osmotic diarrhea is a common adverse effect); target: serum magnesium > 0.6 mmol/l)
- In severe symptomatic cases intravenous infusion of $MgCl_2$ or $MgSO_4$ is suggested
- Potassium sparing diuretics, such as spironolactone, eplerenone (50 mg \times 2/d) or amiloride (up to 20 mg/d); special care to avoid natriuresis and hypotension is mandatory
- Other drugs like renin angiotensin system blockers; however increased natriuresis associated with hypotension is a common side effect
- Non-steroidal anti-inflammatory drugs or COX-2 inhibitors; however long term adverse effects limit their long-term administration

es, intravenous potassium or magnesium infusion is indicated. In some patients with persistent hypokalemia, potassium sparing diuretics, such as amiloride, spironolactone or eplerenone can be administered [35-37]. Other drugs, such as renin angiotensin system blockers or non-steroidal anti-inflammatory agents have been used in case reports [36,38,39]. Chronic hypokalemia-induced interstitial nephropathy increases the risk of chronic renal failure that requires clinical and laboratory monitoring. Finally, special care is indicated in pregnant women with Gitelman syndrome as well as in patients undergo-

ing anesthesia because in these populations electrolyte derangements increase complications risk [40,41]. The family character of the affection should lead clinicians to also test family members of patients with Gitelman syndrome (Table 5).

Conflict of Interest

This review was written independently. Professor MS Elisaf reports personal fees from ASTRA ZENECA, grants and personal fees from MSD, personal fees from PFIZER, ABBOTT, SANOFI, BOEHRINGER INGELHEIM, ELI LILLY, GSK. The authors have given talks and attended conferences sponsored by various pharmaceutical companies, including Bristol-Myers Squibb, Pfizer, Lilly, Abbott, Amgen, AstraZeneca, Novartis, Vianex, Teva and MSD.

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