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Review

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Gitelman syndrome: pathophysiological and clinical aspects*

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Summary

Giltelman syndrome (GS) is a recessive salt-losing tubulopathy of children or young adults caused by a mutation of genes encoding the human sodium chloride cotransporters and magnesium channels in the thiazide-sensitive segments of the distal convoluted tubule. The plasma biochemical picture is characterized by hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis and hypereninemic hyperaldosteronism. However, patients with GS present some clinical and biochemical alterations resembling that observed in thiazide diuretics abuse. On the pathophysiological point of view, GS represents a useful and interesting human model to better understand the clinical consequences of plasma hydro-electrolytes and acid–base derangements, associated with multiple hormonal alterations. The impact of this complex disorder involves cardiovascular, muscle–skeletal and some other physiological functions, adversely affecting the patient's quality of life. This review tries to summarize and better explain the linkage between the electrolytes, neurohormonal derangements and clinical picture. Moreover, the differential diagnosis between other similar electrolyte-induced clinical disorders and GS is also discussed.

Introduction

In 1966, Gitelman *et al.*[1] described a familial disorder characterized by hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis and hypereninemic hyperaldosteronism. Further studies showed that the Gitelman syndrome (GS) was caused by mutation of genes encoding human sodium chloride (NaCl) and magnesium (Mg) transporters in thiazide-sensitive segments of cortical distal nephron.[2,3] The prevalence of GS is estimated to range around 25 cases per 1 million gp while the prevalence of heterozygous subjects is ~1% in the Caucasian population.[4]

Etiology

GS is an autosomal recessive tubular disorder induced by mutations of some genes encoding the NaCl and Mg carriers in the apical membrane of the distal convoluted tubular cells (DCC), which

are responsible for 7–10% of electrolyte tubular absorption.[5] The mutations involve the SLC12A3 gene, which encodes the thiazide-sensitive NaCl cotransporter (NCC). There is a large inter- and intra-familial phenotype variability without any relationship between the clinical severity and type of mutations in the SLC12A3 gene.[6] However, the mutation of nature and/or position of the SLC12A3 gene combined with male gender seems to be associated with the severity of the syndrome.[7] Other genes expressing proteins that promote the distal tubular Mg transport are the cation channels subfamily 6 of the protein Claudin 16 (TRPM6) and a recently identified epidermal growth factor, which acts as a distal regulator of TRPM6 activity.[8] Mutations of these genes interfere with TRMP6 activity with consequent urinary Mg wasting and hypomagnesemia.[9] Of note, most patients with GS and SLC12A3 mutation of one allele suffer from arterial hypotension.[10]

As GS is an autosomal recessive trait, the risk of transmitting the disease from parents to offspring is 25%. Physicians must bear in mind that a child of a GS patient may be apparently free of symptoms in infancy, but the clinical syndrome can appear later at an adult age. DNA analysis is recommended in siblings of a child affected by GS. In view of the good prognosis of GS, antenatal diagnosis is not advised.[4]

Clinical picture

GS is often observed in young adults with normal growth complaining of muscular cramps and weakness associated with mild-to-severe reduction in daily work activity. Many patients suffer from arterial hypotension. However, there are large variations in the severity of symptoms between patients. Some subjects are asymptomatic or present mild weakness, whereas others show severe neuromuscular symptoms such as muscle weakness, paresthesias, cramps and episodes of tetany or paralysis. Epidemiological studies reported that ~6% of GS patients suffer from hypokalemic paralysis, the symptom being more common in Asian patients.[11,12] Some patients may have joint pain attacks, whereas others complain of constipation, polyuria and nicturia. In a questionnaire, increased thirst with abnormal water appetite, associated with salt craving, was the prominent symptom affecting 3/4 of GS patients; the symptoms began in the childhood and persisted in the adulthood.[13] Besides salt craving, many GS patients were eager of pickle brine, salted cucumbers, oranges and lemons. Cases of chondrocalcinosis and nephrocalcinosis have also been reported.

The main electrolyte abnormalities in GS include increased urinary excretion of magnesium and potassium, hypocalciuria, hypomagnesemia, hypokalemia and metabolic alkalosis. Many symptoms are related to these electrolyte abnormalities. However, not all the patients with severe electrolyte abnormalities have clinical symptoms and vice versa. Some patients with severe hypomagnesemia may be asymptomatic, while others with mild hypokalemia can present episodes of paralysis or cardiac arrhythmias.[6]

Pathophysiology of electrolyte disturbances

The renal handling of Mg, Ca, Na and Cl ions depends on a complex molecular activity of specific distal tubular channels. Disruption of this activity can lead to severe electrolyte wasting.[14] It should be noted that a phenotypic variability of GS has been reported in some family members presenting identical genetic defects. The occurrence of electrolyte abnormalities seems to be typical for females with GS, whereas men of the same family show electrolyte disturbances more compatible with Bartter-like syndrome.[6] Moreover, significant differences in the urinary proteomic pattern between normal and GS patients have been recently found. A moderate alteration in several protein expression (S100 family, Rab-GTPase family, aquaporin2, calbinine, megalin and cubilin) is associated with water and electrolyte transport impairment.[15]

Magnesium and calcium abnormalities

After absorption from the intestinal tract, Mg ions are freely filtered by the glomeruli. About 10% of filtered Mg is absorbed by the proximal tubule, while a major amount, 50–70%, is absorbed in the ascending limb of Henle's loop via paracellular passive diffusion. Finally, there is a distal active transcellular Mg reabsorption that depends on epithelial Mg TRPM6 channels. This last site of renal tubular Mg transport has a pivotal role in regulating the urinary electrolyte excretion rate.[16] Therefore, the plasma Mg level is resultant of a balance between the intestinal absorption and renal excretion, both of which are regulated by the TRPM6 channel expression.

Ca ions are also filtered by glomeruli but their tubular handling is quite different. The filtered

Ca ions are absorbed in the proximal tubule and in the ascending limb of Henle's loop via the paracellular pathway by the electronegative transcellular gradient induced by chloride–sodium transport. The transport of active transcellular Ca ions only occurs in the distal convoluted tubules and is driven by parathyroid hormone (PTH) and Vitamin D.

The relationship between Ca and Mg in GS is complex and not completely elucidated. The discovery of a mutation of chromosome 9q.21.13 encoding the TRPM6 Mg channels in families with hypomagnesemia and secondary hypocalcemia has allowed us to identify a defective expression of TRPM6 Mg-permeable channels, localized not only at the apical domain of the distal convoluted tubule but also at the brush border of duodenal Mg transporter cells. Since GS patients present a gene mutation responsible for a reduced expression of TRPM6 Mg channels, it is likely that a downregulation of both intestinal and distal tubular TRPM6 Mg channels may induce intestinal and urinary Mg wasting leading to hypomagnesemia in GS.[17]

However, the pathogenesis of hypocalciuria and its possible linkage with hypomagnesemia in GS and in HCTZ-treated patients still remains debated.

Nijenhuis *et al*.[18] showed that in HCTZ-treated mice hypocalciuria occurred only when diuretic induced hypovolemia. The extracellular volume contraction would activate the sympathetic nervous system and promote a proximal Na and water hyper-absorption that would induce an electrostatic intraluminal positive potential driving a paracellular proximal Ca absorption. According to these results, in HCTZ treated and in GS patients, hypocalciuria would derive from a proximal Ca hyper-absorption rather than a distal Ca handling.

Other experimental investigations reported that the acute intra-tubular HCTZ infusion decreases the expression of the apical NaCl co-transporters with a consequent abrupt intracellular Ca passive diffusion that can induce a distal convoluted cell (DCC) apoptosis, and a reduction of DCC absorptive surface area in that particular tubular segment where the expression of TRPM channels regulates the Mg absorption.[19,20]

If these experimental data may be translated to humans, they would offer a unifying model explaining the possible linkage between the hypomagnesemia derived from urinary magnesium wasting and hypocalciuria. Indeed, a DCC cell mass reduction might be even more relevant in GS and HCTZ-treated patients in whom a chronic inhibition of apical NaCl co-transporters expression occurs and might be responsible not only of a reduced distal Mg transport, but might also induce an up-regulation of calcium transport in the segments downstream to the DCC.[21]

Hypomagnesemia can also impair the function of calciotropic hormones. The inverse relationship between plasma-ionized calcium, PTH and calcitriol was found to be down-regulated in GS patients suggesting that they have a reduced skeletal sensitivity to PTH and an impaired intestinal calcium transport in spite of normal calcitriol plasma levels.[22] This blunted response may also explain the lack of hypercalcemic response to hypocalciuria in GS patients and the recovery of the normal correlation between plasma-ionized Ca and calciotropic hormones after plasma magnesium correction.[23]

The hypomagnesemia-induced lower intestinal and skeletal sensitivity to the calciotropic hormones is confirmed by the different behavior of calcium pool observed in chronic HCTZ-treated subjects and in GS patients. In the former group, hypocalciuria is followed by a calcium-pool expansion with an increase of the calcium bone content, whereas in GS patients hypocalciuria does not induce any change of the bone mineral content. Moreover the lack of parathyroid hyperfunction is confirmed by normal levels of both plasma phosphate and urinary fractional phosphate excretion.[22]

However, hypomagnesemia is not the only promoter of calcium abnormalities in GS. An important role is also played by metabolic alkalosis, which may be caused by a number of factors. By increasing the proximal tubular bicarbonate threshold, hypovolemia promotes metabolic alkalosis.[24] On the other hand, the hypokalemia leading to a K-depletion is likely concomitant with intracellular H^+ repletion that, in response to distal Na absorption, may induce a preferential H^+ urinary secretion causing 'paradoxical aciduria'.[25] Moreover, chronic hypokalemia is also responsible for an increase of urinary ammonia excretion.[26]

Metabolic alkalosis, by inducing a release of the negatively charged protein sites, can favor a shift of circulating plasma-ionized Ca to these protein loci. Their availability is further increased by the hypovolemia-induced plasma protein increase and by the hyperconcentration of negatively charged albumin receptors. Moreover, plasma bicarbonate excess promotes a major calcium complexation, that reduces the fraction of circulating ionized calcium.[22] The chondrocalcinosis may be related to a reduction of pyro-phosphatase activity caused by hypomagnesemia. Impaired enzymatic activity could promote pyrophosphate salt crystallization in periarticular sites and cause the onset of gout-like joint pain.[27]

Sodium and potassium abnormalities

As a consequence of distal tubule escape, the large amount of sodium and chloride delivered in the cortical collecting tubules stimulate the aldosterone-driving transcellular Na across epithelial Na channels of the principal cell luminal membrane. In contrast, the K secretion occurs through the apical K channels.[28] The tubular Na transport generates an electronegative transmembrane voltage that is neutralized either by Cl-transmembrane diffusion across the paracellular pathway or by a coupled K^+ and H^+ ion cellular secretion can eventually lead to metabolic alkalosis and further aggravation of hypokalemia.[29]

Magnesium and potassium homeostasis are closely related, so that potassium depletion cannot be corrected until correction of Mg deficiency that should restore the apical potassium channel function. Moreover the Mg depletion associated with hypokalemia may increase the digoxin toxicity with higher risk of cardiac arrhythmias, but may protect from the onset of tetany.[30]

Chronic severe hypokalemia may also be responsible for severe tubulo-interstitial damage, inducing a Henle's loop dysfunction with abnormally high Na, –Cl and Ca delivery to the cortical collecting duct at a rate exceeding its reabsorption capacity. This abnormality would explain why in some GS patients hypocalciuria may not be demonstrable.

Renin–angiotensin–aldosterone system

Besides the increased NaCl delivery at the macula densa in GS patients, the effective low extracellular volume can also activate the renin–angiotensin–aldosterone system. However, changes of kalemia are *per se* relevant for modulating the aldosterone synthesis from adrenal cortical cells. The inter-individual distal tubular response to aldosterone activity seems to be dependent on the amount of Cl load available for the paracellular transtubular diffusion and from the ratio of apical K channel expression to neutralize the transmembrane electronegativity induced by Na transport.[29]

Connection between pathophysiology and clinical picture

Although the occurrence of *muscular cramps, tetany, paresthesias, joint and muscle pain* are usually related to hypomagnesemia, metabolic alkalosis may also cause some metabolic calcium derangements and explains these symptoms. In fact, despite normal values of total plasma calcium concentration, the concomitant increase of plasma bicarbonate levels with a reduction of circulating acid radicals, usually buffered by the negatively charged plasma protein, makes the negative protein charges free and available. This event induces a shift of circulating ionized calcium ions to negative free charged protein loci, with consequent reduction of the ionized plasma calcium concentration. So an abnormal increase of the muscular tone, ranging from mild weakness and fatigue to muscular cramps, tetanus, paralysis and rhabdomyolysis, may occur.

Fatigue, muscle weakness, constipation, cardiac arrhythmias *and* derangement in urinary concentration capacity, leading to polyuria and nicturia, may be accounted for by hypokalemia. These disturbances are related to the disruption of tubular cells associated with interstitial fibrosis as a long-term consequence of chronic hypokalemia.[31] The muscular weakness is due to low intracellular potassium leading to altered repolarization.

Arterial hypotension is usually associated with the extracellular volume depletion caused by urinary water and electrolyte wasting.[32] Such a condition may enhance weakness, fatigue and muscular cramps. Patients with more severe urinary electrolyte wasting present chronic hypovolemia as evidenced by higher plasma hemoglobin and total protein levels, arterial hypotension, with a consequent renin–angiotensin axis overstimulation. This picture is similar to that observed in normal subjects after thiazide diuretic abuse.

Polydipsia may be caused by the overstimulation of the renin–angiotensin axis in response to the increased delivery of distal tubular sodium at the macular zone and/or to the stimulation of baroceptors from hypovolemia.

Although most subjects with GS show *arterial hypotension*, increased blood pressure values have been found in Amish kindred adult GS patients, despite the demonstration of increased urinary sodium excretion. The available data suggest that a variability of gene mutation may express variable behavior of blood pressure[10] and that other unknown factors, such as urinary sodium excretion, may play a relevant role in regulating arterial pressure.[33]

Cardiac arrhythmias may occur in patients with GS. Bettinelli *et al.*[34] reported that ~50% of GS patients present a slightly or moderately prolonged QT interval. It is well known that hypokalemia associated with hypomagnesemia may prolong the duration of cardiomyocyte action potential. Nevertheless in the majority of cases, this event is

not followed by relevant cardiac arrhythmias. In fact there are only few reported cases of sudden cardiac arrest.[35,36] However, palpitation episodes are reported in 62% of GS patients.[13] Bettinelli *et al*.[34] and Foglia *et al*.[36] found that patients presenting QTc interval >500 ms and a history of syncope are at risk of developing ventricular arrhythmias. Within the cardiomyocytes, K channels generate repolarizing currents by extruding K ions from cells; this mechanism can restore the negativity inside the cell shortening the depolarization. In hypokalemia, the predominance of Na currents produced by the intracellular Na shift prolongs the depolarization (long QTc). The similar plasma potassium, magnesium and bicarbonate levels in patients with normal and in those with prolonged QT interval suggest that the altered ventricular repolarization is linked more to concentration gradients across the cardiomyocytic membrane than to the extracellular absolute levels, thus explaining the lack of peculiar markers of hypokalemia. According to the authors, other electrocardiographic features of hypokalemia and hypomagnesemia (U-wave >1mm, ST depression >0.5 mm, flattened T) were never observed in GS patients. The occurrence of serious cardiac arrhythmias in patients with severe chronic hypokalemia (plasma potassium between 2.6 and 3.4 mmol/l) or hypomagnesemia (plasma magnesium between 0.50 and 0.70 mmol/l) may be triggered by acute events that exacerbate hypokalemia, such as diarrhea or vomiting, or by alcohol abuse, a well-recognized cause of hypomagnesemia, and/or by drugs prolonging the QT interval, such as antihistamines, macrolides, antifungal, psychotropics, β2-agonists, cisapride.[36] These data support the hypothesis that cardiac screening is advisable in GS patients in order to identify the possible factors triggering severe arrhythmias and anomaly of cardiac function.[36]

Differential diagnosis

Diagnosis of GS is often made on the discovery of severe hypokalemia unexplained by the use of diuretics or laxatives in a patient complaining of fatigue, cramps or arterial hypotension. Further investigations into electrolyte and acid–base metabolism demonstrate the presence of hypocalciuria and hypomagnesemia with metabolic alkalosis. However, these electrolyte disorders can also be seen in other disorders, i.e. in patients with HCTZ abuse, in patients with functional and/or organic disorders of calcium and magnesium metabolism, in hyperthyroidism and in familial or sporadic periodic paralysis.

In patients with diuretic abuse, the sodium chloride co-transporter and magnesium channels (TRPM6), located at the apical levels of the distal collecting duct, are inhibited by thiazides. Clinically, this abnormality in the distal sodium, calcium and magnesium tubular transport is very similar to that seen in GS where there are mutations of the genes encoding TRPM6.[23] The differential diagnosis is mainly based on a careful interrogation of the patient, keeping in mind that in an unknown number of cases diuretics are taken secretly by young women to lose weight. Diuretic screen in the urine may be helpful in difficult cases. In this context, the urinary increase in Na^+ and even more in Cl^- excretion in response to the HCTZ load allows us to distinguish with high sensitivity and specificity GS patients who have a blunted response of urinary Cl^- fractional excretion increase from patients with Bartter syndrome and diuretic abuse who have a significant increase of electrolyte excretion. This test may be considered as a diuretic screen to perform a correct diagnosis of GS avoiding heavy workup time and cost of genotyping studies.[37] Moreover the prompt natriuresis with concomitant hypercalciuria in response to furosemide infusion may also represent a useful diagnostic tool to better identify patients with GS from the other tubular diseases with spontaneous urinary NaCl wasting, such as Bartter syndrome.[38] However, the differential diagnosis between GS and Bartter syndrome is more a semantic than a clinical issue, as GS may be considered a mild adult form of Bartter syndrome. Genetic analysis may differentiate between the two syndromes.

In patients with laxative abuse, there is usually a metabolic acidosis with urine potassium/creatinine ratio <1.5.

Metabolic alkalosis with increased urinary potassium excretion and hypertension may be seen in primary hyperaldosteronism, Cushing syndrome, congenital adrenal hyperplasia, renal artery stenosis or Liddle syndrome. The diagnosis rests upon the measurement of blood magnesium, aldosterone and renin levels, response to spironolactone and amiloride, measurement of plasma cortisol level and the urinary cortisol–cortisone ratio.

Reduced plasma-ionized calcium and magnesium levels may be the consequence of post-surgical hypoparathyroidism, usually associated with hyperphosphatemia. A primary defect of parathyroid cellular receptors, insensitive to PTH, is often associated with an abnormally high plasma level of the hormone (pseudohypoparathyroidism also called 'hyper-hypoparathyroidism').

Another functional defect inducing muscular cramps is the so-called spasmophilia, a condition

related to the episodic emotional hyperventilation inducing respiratory alkalosis with a low-ionized calcium level, despite the normal total plasma calcium concentration. The mechanisms inducing muscular contractions in spasmophilia seem to be similar to those observed in GS patients with metabolic alkalosis.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis, familial hypomagnesemia with secondary hypocalcemia, autosomal dominant hypomagnesemia with hypocalciuria and autosomal recessive hypomagnesemia are also caused by mutations in renal ion channels and transporters and can lead to syndromes similar to GS. Genetic testing is useful in doubtful cases.[14]

In advanced chronic renal failure, the defective Vitamin D synthesis is followed by hypocalcemia, which is often associated with metabolic acidosis, rather than alkalosis. The excess of circulating acid radicals induces a shift of these protons to negatively charged proteins with a release of previously bound ionized calcium. This event induces an increase of ionized calcium plasma concentration, which protects the patient against muscular cramps and tetany. Symptoms may appear, however, when metabolic acidosis is corrected too rapidly by massive bicarbonate infusions. This can induce a sudden shift-back of calcium to the protein loci leading to a rapid fall in plasma-ionized calcium.

Prognosis

The prognosis of GS is generally good, but a few patients may be at risk of developing cardiac arrhythmias. Patients with severe hypokalemia are susceptible to cardiac arrhythmias, which may even be life threatening, when joined with severe hypomagnesemia and alkalosis. Also nonadherence to the recommended care regimen may be a further cause of arrhythmia, favoured also by concomitant gastrointestinal troubles.[35] Scognamiglio *et al.*[39] showed that physical exercise may induce coronary microvascular and myocardial defects in GS patients. Thus, an in-depth cardiac assessment is strongly recommended to identify patients at risk of malignant arrhythmias. This finding may challenge the idea that GS is a benign disease. As well as for patients with long Q-T syndrome, competitive sports should be avoided because sudden death can be precipitated by intense physical activity that induces potassium and magnesium loss by sweating.

Independent of the life-threatening risks, GS can affect the quality of life. An evaluation of symptom-related quality of life in GS has been reported by Cruz *et al.*[13] in a series of 50 adults in whom the diagnosis was confirmed by genetic studies. The results of the questionnaire indicated that the great majority of patients complained of mild-to-moderate weakness and fatigue, which negatively affected their quality of life.

Treatment

The treatment of GS is mainly addressed to correct the hydro-electrolyte abnormalities. Correction of hypokalemia may need large amounts of potassium chloride, up to 10 mEq/kg in children and 500 mEq/day in adults.[40] It is mandatory to use potassium chloride because other potassium salts, linked with poorly absorbable anions such as gluconate or aspartate, do not correct hypokalemia and can even worsen the metabolic alkalosis. In fact, by increasing the luminal electronegativity and promoting the distal potassium and hydrogen ions excretion, the poorly absorbable anions worsen the hypokalemic alkalosis. Inversely, the distal paracellular diffusion of chloride ions reduces the K^+ and H^+ ion secretion by reducing the luminal electronegativity. The main problem with the use of potassium chloride is represented by its poor gastric tolerance. Because patients with GS have normal urinary PGE2 excretion, the use of PGE2 synthetase inhibitory drugs is not indicated.[41]

Potassium-spared distal diuretics such as amiloride (5–10 mg/1.73 m^2/day) and spironolactone (200–300 mg/day) may be effective in ameliorating hypokalemia and hypomagnesemia. Colussi *et al.*[42] demonstrated that at the above-reported dosages spironolactone has a greater effect in increasing kalemia and reducing urinary magnesium excretion than amiloride. In normotensive patients both drugs induce an asymptomatic extracellular volume contraction, as shown by significant increases in renin and aldosterone plasma levels. However, in hypotensive patients these drugs should be administered with caution. Ace-inhibitors or angiotensin-receptor blockers may be useful but can aggravate arterial hypotension; their use should be limited to subjects with normal blood pressure.

Treatment of hypomagnesemia is also difficult. High doses of magnesium sulfate or oxide may cause diarrhea. Magnesium chloride is better tolerated and can be used at a daily dosage of 4–5 mg/kg/day divided into 3–4 doses in order to avoid diarrhea.

Conflict of interest: None declared.

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