Gitelman syndrome associated with chondrocalcinosis and severe neuropathy: a novel heterozygous mutation in *SLC12A3* gene

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SUMMARY

Gitelman syndrome (GS) is an inherited salt-wasting tubulopathy characterized by hypocalciuria, hypokalemia, hypomagnesemia and metabolic alkalosis, due to inactivating mutations in the *SLC12A3* gene. Symptoms may be systemic, neurological, cardiovascular, ophthalmological or musculoskeletal.

We describe a 70 year-old patient affected by recurrent arthralgias, hypoesthesia and hyposthenia in all 4 limbs and severe hypokalemia, complicated by atrial flutter. Moreover, our patient reported eating large amounts of licorice, and was treated with medium-high dosages of furosemide, thus making diagnosis very challenging. Genetic analysis demonstrated a novel heterozygous mutation in the *SLC12A3* gene; therefore, we diagnosed GS and started potassium and magnesium replacement.

GS combined with chondrocalcinosis and neurological involvement is quite common, but this is the first case of an EMG-proven severe neuropathy associated with GS. Herein, we underline the close correlation between hypomagnesemia, chondrocalcinosis and neurological involvement. Moreover, we report a new heterozygous mutation in exon 23 (2738G>A), supporting evidence of a large genetic heterogeneity in this late-onset congenital tubulopathy.

Key words: *Gitelman; chondrocalcinosis; tubulopathy; neuropathy.*

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INTRODUCTION

Gitelman syndrome (GS) is a disorder characterized by hypocalciuria, hypokalemia, hypomagnesemia and metabolic alkalosis, due to inactivating mutations in the *SLC12A3* gene that encodes the thiazide-sensitive sodium-chloride cotransporter (NCCT) in the distal convolute tubule. To date, more than 400 mutations of *SCL12A3* gene have been identified (1). Patients may be homozygous, compound heterozygous or, less commonly, heterozygous (2).

Its prevalence is estimated at 1:40,000 (3), making it one of the most frequent congenital tubulopathies. The cornerstone of GS treatment is K+ and Mg2+ supplementation, associated to potassium-sparing diuretics.

CASE REPORT

We describe a 70 year-old male patient who came to our department for severe weight loss, myalgias, recurrent arthralgias and muscle weakness. His medical history revealed primary generalized osteoarthritis, hyperuricemia, type 2 diabetes mellitus, hypertrophic cardiomyopathy due to hypertension, and transient ischemic attack. He was treated by his general practitioner

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with furosemide, metformin, allopurinol and bisoprolol.
For his cyclic joint pain, he had previously been evaluated by another rheumatologist, who suspected chondrocalcinosis and suggested 25 mg of prednisone/day with a tapering scheme and colchicine 1 mg/day, which had proved ineffective.
Physical examination performed during the hospitalization was unremarkable, except for hypoesthesia and hyposthenia in all 4 limbs. Blood pressure was normal. Blood tests showed severe hypokalemia, hypochloremia, hypomagnesemia, metabolic alkalosis and slightly elevated plasma renin activity. Urinalysis showed hypocalciuria, hypophosphaturia, hypochloriduria and hyperkaliuria (Table I).

Table I - Laboratory analyses.

PARAMETER	VALUE	REFERENCE RANGE
CRP	0.84 mg/dL	<0.5
Hemoglobin	12.1 g/dL	14-17.5
Hematocrit	35.2%	40-52
Glycemia	134.2 mg/dL	60-110
Azotemia	61.4 mg/dL	9-23
CPK	385 UI/L	32-294
Myoglobin	341.79 ng/mL	0-110
Serum calcium	10.3 mg/dL	8.3-10.6
Serum phosphate	3.1 mg/dL	2.7-5.1
Serum chloride	67 mmoL/L	98-109
Serum magnesium	1.01 mg/dL	1.3-2.7
Serum potassium	1.7 mmoL/L	3.5-5.5
Serum sodium	132.5 mmoL/L	132-146
Arterial blood pH	7.565	7.32-7.42
Bicarbonate	46.8 mmoL/L	22-26
Urine calcium	51.7 mg/24 h	100-300
Urine phosphate	12.1 mg/24 h	400-1300
Urine magnesium	53.9 mg/24 h	73-122
Urine chloride	13.2 mmoL/24 h	
Urine potassium	48.6 mmoL/24 h	
Urine sodium	26.2 mmoL/24 h	
Plasma renin activity	4.1 ng/dL	0.1-2.4 ng/dL
Aldosterone	50 pg/mL	30-150
ACTH	8 pg/mL	5-50
Serum cortisol	180 ng/mL	150-250
Urine cortisol	40 ug/24 h	10-85
ANA, ENA, ANCA	Negative	

The second day after admission, the patient reported palpitations: an electrocardiogram was performed and disclosed atrial flutter, for which anticoagulant therapy was promptly started. Oral therapy with potassium chloride (KCl) was also commenced, until serum electrolytes returned to normal.
Ultrasonography detected hyperechoic aggregates in the menisci and triangular fibrocartilage of the wrist, features which were deemed to be suggestive of chondrocalcinosis: knee and wrist x-rays confirmed chondrocalcinosis. Four limb electromyography (EMG) demonstrated axonal motor and sensitive neuropathy.
Suspecting a salt-losing tubulopathy, genetic analysis was performed: a novel point heterozygous mutation in the *SCL12A3* gene (Exon 23 NM_000339.1:c.2738G>A,p.Arg913Gln) was found, hence we were able to diagnose Gitelman syndrome.
The patient was eventually discharged, with magnesium supplementation, KCl, potassium kanreonate and tapering furosemide. Despite the lack of a definite diagnosis, which was provided by genetic analysis only few weeks after discharge, therapy was not delayed. We also recommended abstinence from licorice consumption, of which our patient reported eating large amounts.
An ophthalmological evaluation for sclerochoroidal calcification was negative.

DISCUSSION AND CONCLUSIONS

GS belongs to the spectrum of salt-losing tubulopathies, together with Bartter's syndrome (BS). However, BS usually has an earlier age of onset, often presenting in neonates with polyhydramnios, hypercalciuria and growth retardation, whereas GS is poorly symptomatic and symptoms are often non-specific, so it is usually diagnosed during adolescence or adulthood. Nevertheless, some patients with BS may have a late presentation, without hypercalciuria (4).

Symptoms of GS may be systemic, neurological, ophthalmological (5), cardiovascular [arrhythmia, pericarditis (6)], or musculoskeletal (cramps, muscle weakness, joint pain) (7).
The latter is often due to calcium pyrophosphate deposition (CPPD), and an acute pseudogout attack may be the first or only symptom of GS. This condition may be severe, with an involvement of cervical spine (8), and familiar clusters are reported (9).
CPPD in GS seems to be strictly related to hypomagnesemia, which is caused by inhibition of TRMP6 channel, Mg2+ permeable channel located close to NCCT. Hypomagnesemia is well known as a trigger of pseudogout attack: first, it may induce CPPD (Mg2+ is a cofactor for pyrophosphatases, enzymes that catalyze the hydrolysis of organic pyrophosphate, increasing their solubility), secondly many other conditions leading to hypomagnesemia [short bowel syndrome (10), tacrolimus or ciclosporin therapy (11)] are associated with CPPD. Moreover, although BS was first described in association with pseudogout, no cases were described in BS without hypomagnesemia (12): we may suppose that they could have been cases of GS misdiagnosed as BS (13).
Although rare, this condition may be easily diagnosed, but clinicians should obtain a careful medical history. For instance, licorice and furosemide are both common pitfalls in the differential diagnosis of GS.
The first one contains glycyrrhizin, which inhibits 11-beta-hydroxysteroid dehydrogenase type 2: normally, this enzyme oxides cortisol to cortisone, preventing the activation of the mineral-corticoid receptor by cortisol, whose serum levels are up to 1000 times greater than aldosterone. Thus, licorice indirectly leads to hypokalemia, metabolic alkalosis, hypertension and suppressed serum levels of renin and aldosterone (14).
By contrast, loop diuretics inhibit Na-K-Cl cotransporter and lower blood pressure reducing serum sodium and potassium, eventually leading to hypomagnesemia, hypocalcemia, high levels of plasma renin activity and aldosterone.
Our patient reported eating large amounts of licorice, especially during the last weeks, and was treated with medium-high dosages of furosemide, thus making diagnosis very challenging. Blood pressure, usually low in GS and diuretic therapy, was counterbalanced by the consumption of licorice, and serum aldosterone, elevated in GS and furosemide, was apparently normalized by the mechanism of action of glycyrrhizin.
Hyperkaliuria, hypocalciuria and genetic analysis helped us to make the right diagnosis, but we can suppose that both furosemide and licorice contributed to the severe hypokalemia, recently worsened by the increased consumption of candies by the patient.
Our case report underlines the close relationship between hypomagnesemia and CPPD, not only in GS: in our opinion, a routine evaluation of serum level of Mg2+ should be always performed in patients with pseudogout, since the correction of this electrolyte disorder may contribute to achieve a therapeutic response. We suggested an ophthalmological evaluation too, as an association of CPPD and sclerochoroidal calcification has been described (10).
Secondly, to our knowledge this is the first described case of an EMG-proven severe neuropathy associated with a misdiagnosed chronic hypokalemia. Although neurological involvement is a quite common feature in GS, to date no one has demonstrated the presence of EMG alterations. We postulate that hypomagnesemia may impair the normal nerve trophism, since the importance of Mg2+ in neuroprotection is well described (15).
Finally, we reported a GS with a novel SCL12A3 variation: to our knowledge, this is the very first heterozygous mutation in exon 23 (2738G>A), because the only other case of mutation involving exon 23, described in a Chinese case report, was homozygous and its nucleotide change was 2744 G>A (1). Our findings support evidence of a large genetic heterogeneity in this late-onset congenital tubulopathy.

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