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Unusual association of Gitelman syndrome with early diagnosis and glomerular proteinuria; a case report

Roberto Gutiérrez^{1*}, Marcela Fortunato¹, Carlos Vigliano², María Fernanda Toniolo³, Álvaro Espinoza¹, Pablo Miguel Raffaele¹

¹Unidad Renal, Hospital Universitario Fundación Favaloro, Buenos Aires, Argentina

²Departamento de Anatomía Patológica, Hospital Universitario Fundación Favaloro, Buenos Aires, Argentina

³Centro de Diagnóstico Patológico, Buenos Aires, Argentina

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ABSTRACT

Gitelman syndrome is an autosomal recessive hereditary tubulopathy whose main alteration is at the sodium-chloride symporter in the distal convoluted tubule, characterized by metabolic alkalosis, normotension, hypokalemia, hypomagnesemia and hypocalciuria. Proteinuria and glomerular hyperfiltration (especially at the beginning of clinical course) are not characteristic manifestations of this disease. We present the case of a 25-year-old female with recent diagnosis of Gitelman syndrome who presented with hyperfiltration and glomerular proteinuria, leading to a renal biopsy, which showed hypertrophy of juxtaglomerular apparatus and mesangial proliferation. In electron microscopy focal podocyte detachment was evidenced, which was compatible with secondary focal segmental glomerulosclerosis (FSGS). This case of association of tubulopathy with secondary glomerulopathy of early presentation, shows the final pathway in this disease, when generating sustained renal ischemia due to the increased activity of renin-angiotensin-aldosterone system (RAAS). Renal biopsy and electron microscopy proved to be useful to define prognosis, early recognition of progression and adjust treatment in this patient.

Case Report

Implication for health policy/practice/research/medical education:

Gitelman syndrome is a common cause of tubulopathy, which can be associated with hypertrophy of the juxtaglomerular apparatus. This association can lead to podocyte lesion and therefore proteinuria. An early and timely diagnostic and therapeutic approach would prevent podocyte injury and accordingly, may slow the disease progression.

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Introduction

Gitelman syndrome is an autosomal recessive inherited tubulopathy, which is characterized by metabolic alkalosis, hypokalemia, normotension, hypomagnesemia and hypocalciuria. The disease is manifested mainly in adolescence; however, its diagnosis can be delayed until adult age due to asymptomatic pattern for long periods of time. There are more often case reports of early beginnings in youth without previous manifestations. The prevalence is estimated in about one in 40 thousand people, appearing in 1% of the heterozygous Caucasian population, becoming one of the most frequent inherited tubulopathy disorders (1).

Most cases are caused by mutations in the SLC12A3 gene (presented in chromosome 16q) which encodes

the thiazide-sensitive sodium chloride transporter that is expressed in the luminal region of the distal convoluted tubule. There have been described more than 170 different mutations in SLC12A3 gene and with better detection techniques, while the rate of identification rises also to more than 90% in some series (2,3).

The clinical diagnosis is usually characterized by transient and episodic periods of muscle weakness, facial and limbs paresthesias, with or without abdominal pain, vomits and constitutional symptoms, exceptionally can present seizures, arrhythmia and QT prolongation. Sometimes they are asymptomatic, with normotension or a tendency to be lower. Their growth is normal, although it can be delayed because of severe hypocalcemia and hypomagnesemia (4).

*Corresponding author: Roberto Gutiérrez, Email: mdrobertoguti@gmail.com, mfortunato@favaloro.org

Classically tubulopathies are not related to proteinuria. The few renal biopsies reported in the literature showed juxtaglomerular apparatus hyperplasia, without glomerular or tubular abnormalities (5).

The treatment is about oral magnesium and potassium supplements (potassium chloride) and potassium sparing diuretics (spironolactone and amiloride). However, there is no treatment that could avoid completely potassium depletion and patients cannot reach potassium levels higher than 3.2 to 3.5 mEq/L in a continuous and sustained way, so they oscillate between 2.7 to 3.2 mEq/L but without symptoms.

Case Presentation

A 25-year-old female, without medical history, presents with a 6-month clinical picture based on atypical chest pain (cardiologic cause was discarded) associated with hand paresthesias and hypokalemia (~2.6 mEq/L). She referred to two previous hospitalizations due to similar conditions of hypokalemia (~2.2 mEq/L and 2.6 mEq/L, respectively) treated with intravenous potassium reposition and spironolactone 50 mg/d.

At the initial clinical evaluation, she presented with normotension, laboratories revealed normal serum creatinine (Creat=0.6 mg/dL), moderate hypokalemia 2.6 mEq/L, hypomagnesemia 1.3 mg/dL, aldosterone level in activity 219 ng/mL, renin level in activity 2.8 ng/mL and in resting 0.9 ng/mL (both diminished, notably they were performed after five days of suspending spironolactone) thyroid hormones, collagenogram, viral serologies, and urinary sediment were all normal. Renal ultrasonography and abdominal tomography revealed normal adrenal glands. A 24-hour urine sample showed adjusted creatinine clearance of 149.1 mL/min, proteinuria 550 mg/d, urinary calcium 200 mg/day, urinary potassium 88 mEq/day and urinary sodium excretion of 136 mEq/day (Tables 1 and 2).

We assumed as a Gitelman syndrome characterized by hypokalemia, hypomagnesemia and hypocalciuria. We prescribed potassium supplements orally and intravenous, spironolactone was restarted, she evolved with potassium level fluctuations (highest 3.2 mEq/L) and partial improvement of symptoms.

According to unusual proteinuria and glomerular hyperfiltration, we decided to perform renal biopsy (Figure 1) which reported; Juxtaglomerular apparatus hypertrophy and mesangial proliferation with immune deposits as; IgG + (0 to 4) and IgM +++ (0 to 4), immunohistochemistry for WT1 was positive and by electron microscopy evidenced focal and isolated detached podocyte pedicels associated with sclerosis, which was compatible with secondary focal segmental glomerulosclerosis (FSGS). Afterwards a genetic study was requested.

Table 1. Laboratory data

Parameter	Results
TSH	2.52 mcg/dL
T4	1.09 µg/dL
Aldosterone	219 µg/mL
Cortisol	21.7 µg/dL
C3 complement	104 mg/dL
C4 complement	16 mg/dL
Ferremia	42 µg/dL
Transferrin	340 mg/dL

Table 2. Parameters in 24 hours urine sample

24 Hours urine	Results
Proteinuria	550 mg/d
Creatinine clearance	149.1 ml/min
Calciuria	200 mg/d
phosphaturia	200 mg/d
Potassium	88 mEq/L
Sodium	136 mEq/L
Magnesium	0.52 g/d
Cortisol	27.4 µg/dL

The patient continued with weekly relapses of episodes of symptomatic hypokalemia and after histologic diagnosis, enalapril was initiated 5mg/day associated with spironolactone 50 mg/d and oral potassium and magnesium supplements were increased, with substantial increase in relapse intervals. The patient never suffered from new hospitalization nor severe hypokalemia since the last combination of enalapril and spironolactone.

Discussion

Gitelman syndrome was described for the first time in 1996 by Gitelman et al (6). They described the SCL12A3 gene mutation as a cause of this disease. In scientific literature there are very few case reports of tubulopathies associated with proteinuria. One of the first cases been reported was by Bulucuy et al in 1998, where it was evidenced as a histological finding FSGS in a man of 21 years old with GS, in whom it was conducted a renal biopsy because of chronic hypokalemia and the second case where was described a patient with C1q nephropathy (7,8).

In other case report of an Asian patient with genetic and clinical diagnosis of Gitelman syndrome, was performed a renal biopsy for identification of histological effects of this disorder, finding by optic microscopy, juxtaglomerular apparatus hypertrophy with mesangial extra-glomerular proliferation without glomerular abnormalities (9).

One explanation of this association is the increased

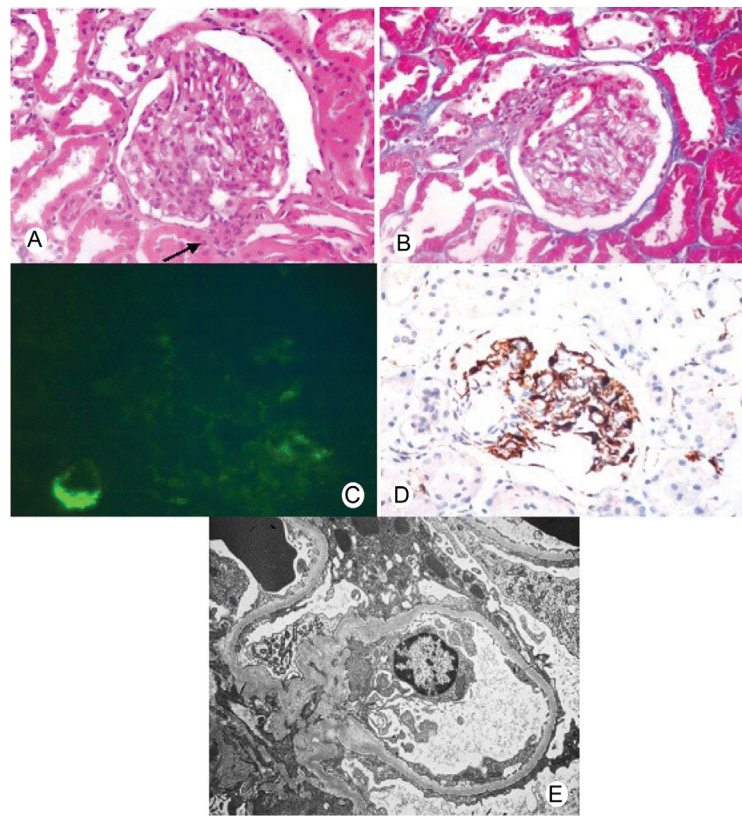


Figure 1. Renal biopsy. Optic M. 10 glomerulus were evaluated. (A) PAS: mesangial expansion and proliferation at the tubular pole adjacent to the dense macula compatible with juxtaglomerular apparatus hypertrophy (arrow). (B) Masson S.: It observes minimum interstitial fibrosis, juxtaglomerular apparatus hypertrophy and arteriolar hyalinization. (C) IIF: deposits of IgM ++/4 in mesangial and vascular. (D) IHC. WT1 positive and (E) Electron M.: detached podocytes in a focal and isolated way compatible with focal and segmental glomerulosclerosis.

expression of renin-angiotensin-aldosterone system (RAAS) and ischemia due to sustained hypokalemia. Hence mesangial proliferation which in turn is in association with podocyuria is an expression of continuous subjection of glomerular structures to intra-glomerular hypertension and exacerbated adaptation mechanisms (10).

The chronic activation of RAAS leads to an increase of local and systemic levels of angiotensin II and renin, consequently causing podocyte lesions. Likewise, angiotensin II can induce proteinuria by different hemodynamic and not hemodynamic mechanisms that involve endothelial vascular growth factor and beta-1 transformation growth factor (11). Proteinuria was also informed in patients with Addison disease, another hyporeninemic condition.

Chronic hypokalaemia may play a role in causing proteinuria, which was demonstrated by Reungini's group, who described mild proteinuria in rats with mild hypokalemia administered normal or moderately low potassium diet, with or without hydrochlorothiazide, which was attributed to secondary hyperaldosteronism as a result of volume exhausted (12).

Although high levels of angiotensin and renin, sodium depletion leads to a chronic decrease in plasma volume

(kidneys cannot reabsorb sodium chloride and excrete large amounts of both electrolytes) which is reflected in tendency to low or normotensive and accompanying a chronic state of mild dehydration (13).

Conclusion

The described data suggests an association of Gitelman syndrome and glomerular proteinuria with abnormal basement membrane findings which probably may not be as a matter of fact a mere coincidence. Recently, impaired renal phosphate management, arterial hypertension and chronic kidney disease have been associated with Gitelman syndrome. Patients with this tubulopathy must be evaluated for early detection of proteinuria and perform a renal biopsy if relevant.

In our case it was presented the association of Gitelman syndrome tubulopathy and histological findings of mesangial proliferation with immune deposits of IgM and FSGS, showing the usefulness of renal biopsy not just for treatment but for prognosis indeed.

Authors' contribution

RG, MF and CV were the principal investigators of the study. MFT, AE and PMR were included in preparing

the concept and design. MF and PMR revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. Informed consent was obtained from the patient for the publication of the report.

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