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Letter to the Editor

# Gitelman syndrome – A new mutation in the SLC12A3 gene

## Síndrome de Gitelman: una nueva mutación en el gen SLC12A3

*Dear Editor,*

Gitelman syndrome (GS) is one of the most frequent inherited renal tubular disorders,[1] and it's caused by mutations in the SLC12A3 gene encoding the thiazide-sensitive sodium chloride cotransporter (NCC) expressed in the apical membrane of distal convoluted tubule (DCT) cells.[2]

We present the case of a 50-year-old caucasian male with persistent hypokalaemia, referred to our nephrology department. This condition had first been found in blood analyses made on an emergency room visit due to a syncope and, until then, monitored in the primary care. In the anamnesis he only refers occasional paresthesias on the lower limbs, denying other symptoms. He has history of a left adrenal nodule (9 mm) stable since 2011 and was on supplementation with 600 mg of potassium chloride twice a day. His family history was negative. On physical examination he had a normal blood pressure, no significant alterations were found.

On biochemical analyses the patient presented persistent hypokalaemia, despite supplementation, hypomagnesaemia and hypochloremia. Serum creatinine, and remainder ionogram were normal. Further investigation revealed elevated plasma-active renin, normal aldosterone, elevated $CO_2$ and hypocalciuria (Table 1).

Abdominal computer tomography revealed normal kidneys and no adrenal nodule was found. The patient started supplementation with magnesium and spironolactone.

Due to high suspicion of Gitelman syndrome, a genetic test was performed using next generation sequencing Ion AmpliSeq Exome Panel (Hi-Q) Kit. The test found an apparent homozygous mutation, c.945del p(Gly316Alafs*54), in the SLC12A3 gene. Sequence map is shown in Fig. 1.

In our first evaluation, we could think about primary hyperaldosteronism as a possible cause for the low serum potassium associated with a left adrenal nodule. However, the patient presented normal blood pressure and the CT was normal.

After the results from further investigation (Table 1) the main differential diagnosis were eating disorders, long-term laxative abuse, thiazide diuretics abuse, and Bartter and Gitelman syndromes.[3] These non-renal causes were excluded by normal urinary chloride excretion, the absence of metabolic acidosis, consistent analysis results over time and normal urinary sodium and potassium excretion.[3] Bartter syndrome was less likely as it is characterized by an earlier onset, associated with growth retardation. Low urinary calcium excretion excluded this tubulopathy.[1] The final diagnose of GS was obtained with the genetic test.

First described by Gitelman et al. in 1966, GS is an autosomal recessive salt-losing renal tubulopathy,[4] in most cases due to inactivating mutations in the gene that encodes the renal thiazide-sensitive NCC present in the epithelial cells of the DCT.[2] With an estimated prevalence of ~25 per million, GS is the most frequent inherited tubulopathy.[1]

It is characterized by hypomagnesaemia, hypocalciuria and secondary aldosteronism, responsible for hypokalaemia and metabolic alkalosis.[4]

Patients usually present above six years of age and in many cases the diagnosis is only made at adult age. Most suffer from tetany, especially during periods of fever or gastrointestinal losses, and paresthesias.[5]

GS is caused, in the majority of cases, by mutations in the solute carrier family 12, member 3, SLC12A3 gene.[1] To date, >160 mutations, including missense, nonsense, frameshift, and splice-site mutations, as well as gene rearrangements, have been documented.[6] Missense mutations are the most frequent, being the IVS9+1G>T reported as the most common mutation in the European population, and frameshift mutations are much fewer.[7]

GS diagnosis is based on the clinical symptoms and biochemical abnormalities above described,[1] and confirmed by genetic test.[8] Our patient presented an apparent homozygous mutation, in the SLC12A3 gene. This variant is found on the gnomAD data base, with an allelic frequency of 1:251374 in the general population, but it has never been identified in homozygoty or in European population, which highlights the relevance of this publication. This is a frameshift mutation on exon 7, which began from the glycine in the No. 316, mutated into alanine, and leading to premature termination of NCC protein, that affects the splicing process and introduces a premature stop-codon (Human Splicing Finder web source was used to predict the possible consequences of the mutation in the splicing process).[9]

The long-term treatment relies on high intake potassium and non-restrictive salt diet, as well as on supplements and other drugs. Lifelong oral potassium and magnesium supplementation are the mainstay of treatment for these patients.[8] In cases of persistent or symptomatic hypokalaemia, the use of potassium-sparing diuretics can be useful, as they increase

**Table 1 – Laboratory investigation.**

| | Patient values | Reference values |
|---|---|---|
| *Complete blood count* | | |
| WBC ($\times 10^3/\mu L$) | 7.63 | 4–10 |
| Haemoglobin (g/dL) | 13.6 | 13.0–17.5 |
| Haematocrit (%) | 37.4 | 40–50 |
| Platelets ($\times 10^3/\mu L$) | 331 | 150–400 |
| *Serum biochemicals* | | |
| Sodium (mmol/L) | 137 | 136–146 |
| Potassium (mmol/L) | **3.1** | 3.5–5.1 |
| BUN (mmol/L) | 2.8 | 1.3–3.5 |
| Creatinine (μmol/L) | 83.1 | 63.65–104.31 |
| Glucose (mmol/L) | 5.3 | 3.3–6.0 |
| Choride (mmol/L) | **98** | 101–109 |
| Calcium (mmol/L) | 2.4 | 2.2–2.6 |
| Phosphorus (mmol/L) | 0.87 | 0.81–1.45 |
| Magnesium (mmol/L) | **0.49** | 0.74–1.07 |
| Albumin (g/dL) | 4.6 | 3.5–5.2 |
| Serum osmolality (mOsm/kg) | 275 | 260–302 |
| $CO_2$ (mmol/L) | **30** | 23–29 |
| Active Renin (uU/mL) | **117** | 7–76 |
| Aldosterone (pg/mL) | 212 | 40–310 |
| Aldosterone to Renin Ratio | 2.17 | <25 |
| *Urine chemistry* | | |
| Urinary volume (mL) | 2400 | |
| pH | 8.0 | 5.0–8.0 |
| Urine specific gravity | 1.010 | 1.010–1.030 |
| Sediment | Inactive | |
| Potassium (mmol/24 h) | 87.6 | 26–113 |
| Sodium (mmol/24 h) | 302.4 | 27–287 |
| Calcium (mmol/24 h) | **4.8** | 15–20 |
| Magnesium (mmol/24 h) | 3.3 | 3.0–5.0 |
| Chloride (mmol/24 h) | 245 | 110–260 |
| Creatinine clearance (ml/min) | 93.5 | 90.0–120.0 |
| Protein (mg/24 h) | 84 | <150 |

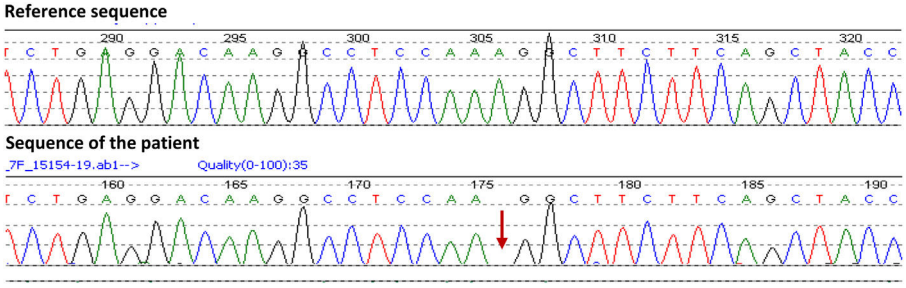


**Fig. 1 – The above sequence column is the reference sequence, next is the sequence of the patient. The mark represents the c.945del p.(Gly316Alafs*54) mutation in apparent homozygoty.**

serum potassium levels and treat magnesium depletion that is worsened by elevated aldosterone levels.[10]

In summary, it would be interesting to study the first-degree relatives to exclude the possibility that the variant found is a heterozygous mutation with deletion of the other allele in this locus. Also, it is important to study the other family members to understand if there is an history of consanguinity that could explain the presence of this rare homozygous mutation and alert to the possibility of other genetic diseases yet to detect.

## Conflict of interest

None.

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# Home haemodialysis, the perfect opportunity to stay at home

## Hemodiálisis domiciliaria, la oportunidad perfecta para quedarte en casa

*Dear Editor,*

In the last decade, the number of patients treated with home haemodialysis (HHD) has increased considerably,[1] and the treatment has seen growing interest worldwide due to the benefits it provides with respect to other options.[2] However, although more and more people opt for this method, currently only an estimated 0.3% of patients of patients on renal replacement therapy (RRT) are treated with this technique. There are some differences between the different autonomous communities in Spain, but in general the number of patients who choose this option remains small.[3]

According to a survey carried out among nephrologists, published in this journal,[4] it has been observed that as HHD programmes are developed, the initial barriers derived from the lack of practical knowledge of the technique gradually disappear, and only those dependent on financial and training resources remain[4] (staff dedicated exclusively to HHD with specific training).

For this reason, it seems appropriate to present our experience performing a retrospective analysis of the patients included in the HHD programme, their characteristics and adverse events suffered from January 2018 to June 2020, at the Haemodialysis Unit of the Torrecárdenas University Hospital (Almeria). In Table 1, we present the characteristics of the five patients included in the HHD programme.

It should be noted that the patients not only complied with an optimised quality treatment guideline, as demonstrated both at an analytical and clinical level, but also patients may adapt the prescribed regimen to each individual case which facilitate work and social integration, continuing with a their life as normal as possible, with their kidney disease.

It is noteworthy that in this high-risk patient profile, HHD prevents exposure and the consequent increase in the incidence of infections related to the healthcare setting, of much greater importance during the SARS-CoV-2 pandemic.[5]

For further justification of the importance and advantage of starting HHD at a time like the one we are currently experiencing, we refer to the official records of the Spanish Society of Nephrology regarding SARS-CoV-2 infection of November 2020, in which it is highlighted that, although the incidence among patients on RRT has grown in the second wave of infection in a similar manner as in the general population, with a decrease in the average age of affected patients (−7 years with respect to the first wave), we should bear in mind that we are dealing with a fragile patient, with an state of immunosup-

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