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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, associ-

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

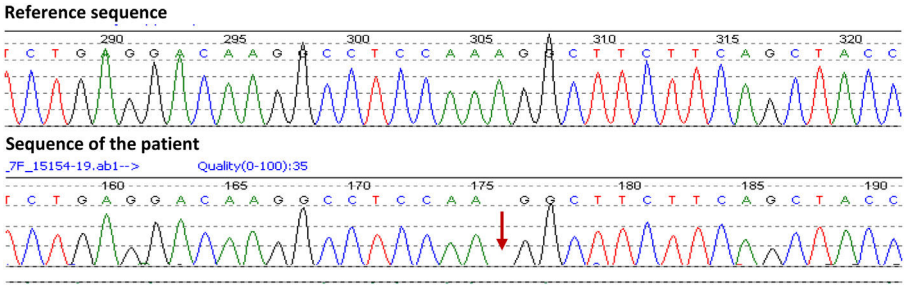

Fig. 1 – The above sequence column is the reference sequence, next is the sequence of the patient. The mark represents the c.945del p.(Gly316Alafs*54) mutation in apparent homozygoty.

ated 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 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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Hemodiálisis domiciliaria, la oportunidad perfecta para quedarte en casa

Home haemodialysis, the perfect opportunity to stay at home

Sr. Director:

En la última década se ha incrementado considerablemente el número de pacientes tratados con hemodiálisis (HD) domiciliaria (HDD)[1], una modalidad de interés creciente a nivel mundial debido a los beneficios que aporta con respecto a las demás[2]. No obstante, aunque cada vez son más los que optan por esta modalidad, actualmente solo se estima en un 0,3% los pacientes en tratamiento renal sustitutivo (TRS) con esta técnica. Con algunas diferencias entre las diferentes comunidades autónomas, sigue siendo un pequeño número el que se decanta por esta opción[3].

Según la encuesta realizada a nefrólogos, y publicada en esta revista[4], se observa que según se desarrollan los programas de HDD, las barreras iniciales derivadas de la falta de conocimiento práctico de la técnica van desapareciendo y quedan únicamente las dependientes de los recursos económicos y formativos[4] (personal dedicado exclusivamente a la HDD, formación específica).

Por este motivo, parece oportuno mostrar nuestra experiencia realizando un análisis retrospectivo de los pacientes incluidos en programa de HDD, sus características y eventos adversos sufridos desde enero de 2018 hasta junio de 2020 en la Unidad de Hemodiálisis del Hospital Universitario Torrecárdenas (Almería). En la tabla 1 presentamos las características de los cinco pacientes incluidos en el régimen de HDD.

Cabe destacar que los pacientes no solo cumplen con una pauta de tratamiento optimizada y de calidad, que se manifiesta tanto a nivel analítico como clínico, sino que pueden adaptar la prescripción de la técnica de manera individual, fomentando la reinserción laboral, social, continuando con una vida lo más cercana a la normalidad posible, dentro de la enfermedad renal.

Es reseñable que la HDD evita, en este perfil de paciente de alto riesgo, la exposición y consecuente aumento de incidencia de las infecciones relacionadas con el ámbito sanitario, de mucha mayor importancia durante la pandemia por SARS-CoV-2[5].

Para mayor justificación de la importancia y ventaja que supone el inicio de esta técnica de TRS en un momento como el que vivimos actualmente, nos remitimos a los registros oficiales de la Sociedad Española de Nefrología sobre la infección por SARS-CoV-2 a fecha de noviembre de 2020, en los que si bien se destaca que la incidencia ha crecido en la segunda ola de infección de un modo similar al de la población general entre los pacientes sometidos a TRS, con disminución de la media de edad de los pacientes afectados (variación de -7 años con respecto a la primera ola), siempre hay que tener presente que nos encontramos ante un perfil de paciente frágil, con una inmunosupresión ligada a la técnica a la que se ven sometidos de manera regular, y de la que derivan muchas otras comorbilidades[6].

Analizando los datos hasta la fecha, durante la primera ola, la hemodiálisis en centros tanto hospitalarios como periféricos es la modalidad de TRS que mayor porcentaje de infecciones por SARS-CoV-2 presenta (60%), seguida de los pacientes trasplantados (37%). La diálisis peritoneal (DP) supone el 2,7% de los casos. Destaca en este punto que la HDD supone solo el 0,5% de los pacientes con TRS infectados. Sin embargo, en la segunda ola, los pacientes trasplantados son los más afectados (49%), algo por encima de los pacientes en hemodiálisis en centro (48%). El 2% de los casos ocurrieron en pacientes en DP y el 1% en HDD. Realizando un resumen global de la infección por COVID-19, se contagió el 5,7% de la población total en hemodiálisis en España vs. 2,6% de los trasplantados renales y el 2% de los pacientes en diálisis peritoneal.