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Gitelman syndrome with hyponatraemia, a rare presentation

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Dear Editor,

Hypokalemia is one of the most common electrolyte abnormalities which etiology can be unclear and the incorrect diagnosis can result in the wrong treatment.

Gitelman syndrome (GS) is an autosomal recessive disorder of the thiazide-sensitive sodium chloride cotransporter, expressed at the distal convoluted tubule (DCT). The mutation is found in the *SLC12A3* gene, but there are also others. Its prevalence is estimated to range 25 cases per 1 million.[1] Acquired GS is rarer and usually associated with autoimmune diseases or after renal transplantation.[2]

GS phenotype is characterized by hypokalemic alkalosis, hypomagnesemia, hypocalciuria, and secondary aldosteronism without hypertension. Hyponatraemia is not a recognised feature of GS.[3]

CASE REPORT

A 34 year old caucasian woman with no prior medical presented with severe hypokalemia; hypomagnesemia and mild hyponatremia. Her past medical and family history were unremarkable. She was on no medication and denied any symptoms, unless for occasionally muscle cramps. Water intake ≥3L/day. She was normotensive, no edemas and normal urine output. The review of systems was otherwise negative.

Table 1 summarizes laboratory investigation.

Patient was managed with oral magnesium and spironolactone 50mg/day. Her condition improved significantly and her last routine lab control showed serum potassium 3.78mmol/L, magnesium 0.79mmol/L and sodium 136.0mmol/L, without any other changes.

DISCUSSION

Potassium excretion is mostly derived from secretion in the distal nephron, driven by an electrochemical gradient increased by aldosterone-induced sodium reabsorption; and by an electroneutral $K^+ Cl^-$ secretory mechanism.[4]

Hypokalemia may result from decreased intake, increased translocation into the cells, or, most often, increased losses in the urine, gastrointestinal tract, or sweat.

Although these causes were sought by history taking and clinical examination, we needed to exclude surreptitious vomiting or drugs abuse because high urinary potassium, metabolic alkalosis and alkaline urine can also be present in these two disorders. Differential diagnosis with vomiting was made through urinary chloride which is low in hypovolemia due to hyperaldosteronism, opposing to patient normal values poiting to a renal disorder. Diuretic abuse was excluded through a negative urinary screen.

Because the patient was normotensive, we stood with Gitelman or Bartter's.

Magnesium excretion rate is regulated by distal reabsorption that depends on epithelial TRPM6 channels, which gene suffers a downregulation mutation in GS, inducing urinary magnesium wasting leading to hypomagnesemia,[5] opposing to Bartter syndrome.

Calcium is absorbed in proximal nephron driven by an electronegative transcellular gradient induced by chloride–sodium transport; and in DCT driven by parathyroid hormone and Vitamin D. Hypocalciuria pathogenesis still remains debated but an important role is played by metabolic alkalosis.[6]

At the end, our patient fulfilled the diagnostic criteria for GS, although few unusual aspects. First, the inappropriately high urine pH and pCO2 (directly proportional to bicarbonate (HCO_3^-) concentration) could be explain through high chloride delivery that enhances HCO_3^- secretion in type A intercalated cells (to maintain electroneutrality). Adding to this, hypokalemia suppresses aldosterone secretion, which reduces sodium reabsorption (no hypovolemia) increasing back-diffusion of hydrogen, allowing the urine to become more alkaline than plasma.[6] Aldosterone activity degree could be accessed through tubular fluid potassium concentration at distal cortical collecting tubule, estimated from transtubular potassium gradient but this would only be usefull in hyperkalemia settings. Additionaly, recente publications found that its assumptions were not valid.[7] Finally, patients with metabolic alkalosis have a respiratory compensation but the beneficial pH effect is blunted when arterial pCO_2 elevation increases renal acid excretion stimulating renal ammoniagenesis, raising urine pH.[6]

Mild hyponatraemia was present and, opposing to diuretic use (excluded), is not a typical feature of GS. After excluding hypothyroidism, adrenal insufficiency and renal failure, hyponatraemia associated to normal volemia, inappropriately high urine osmolality and urinary sodium concentration suggested the presence of a syndrome of inappropriate secre-

Table 1. Results of the laboratory investigation

	Patient values	Normal values
Complete blood count		
WBC (× 10^3/µL)	7.30	4.0-10.0
Haemoglobin (g/dL)	15.60	12.0-16.0
Haematocrit (%)	44.90	36.0-46.0
Platelets (× 10^3/µL)	234	150-400
Serum chemistry		
Sodium (mmol/L)	132	137.0-145
Potassium (mmol/L)	2.23	3.5-5.1
Urea (mmol/L)	4.20	2.5-6.4
Creatinine (µmol/L)	68.50	46.0-92.0
Fasting blood sugar (mmol/L)	4.60	4.9-5.8
Calcium (mmol/L)	2.40	2.10-2.55
Phosphorus (mmol/L)	1.22	0.81-1.45
Magnesium (mmol/L)	0.66	0.7-1.2
Albumin (g/L)	45	35-50
Uric acid (µmol/L)	371	149-506
Calculated serum osmolality (mOsm/kg)	280	270-290
Measured serum osmolality (mOsm/kg)	289	270-290
Osmolol gap	9	8-16
Cortisol (µg/dL)	32	8-25
TSH (mIU/L)	3.9	0.35-6.20
T4L (ng/dL)	1.1	0.45-1.2
Urine chemistry		
Urinary volume (mm)	1,100	
pH	9.0	4.6-8.0
pCO2 (mmHg)	83	
Sediment	Inactive	
Potassium (mmol/24 hr)	73.60	26-113
Sodium (mmol/24 hr)	277.5	27-287
Calcium (mmol/24 hr)	Below the measurable limit	15-20
Magnesium (mmol/24 hr)	5.0	3.0-5.0
Chloride (mmol/24 hr)	259.8	110-260
Creatinine clearance (ml/min)	119.4	90.0-120.0
Urine osmolality (mOsm/kg)	526.6	80-1,200
Protein (mg/24 hr)	Below the measurable limit	<150
Transtubular potassium gradient	18	7-9
Diuretic screen (24 hr sample)	Negative	
Arterial blood gas		
pH	7.50	7.35-7.45
PCO2 (mmHg)	46	35-48
PO2 (mmHg)	118	83-108
HCO3 (mEq/L)	35.90	22.0-31.0
O2 saturation (%)	99	96-100
BE	12.7	-2.0 - +2.0
Sodium (mmol/L)	133.0	136-144
Potassium (mmol/L)	2.13	3.4-4.5

tion of antidiuretic hormone (SIADH). The stimulus for this secretion is unclear. Although chronic hypokalemia could be characterized by some resistance of tube collector cells to ADH, GS has a urinary diluting capacity disturbed creating a *SIADH like effect*. Opposing to Bartters, GS has a preserved concentrating ability,[6] because medullary thick ascending limb is intact. Since there is no hypovolemia, urinary sodium excretion is high to maintain electroneutrality as HCO_3^- is being excreted. Adding to this, in severe hypokalemia, via unknown mechanism, distal chloride excretion is increased causing a paralell sodium waste.

There are only a few cases of GS with hyponatraemia reported and in two of them a combination of high water intake with an impaired urinary dilution capacity caused by GS was described as a possible explanation for *SIADH-like* biochemical features.[8,9] Adding to water, our patient must had a high intake of salt which raised the sodium delivery to the collecting duct and could explain both sodium and HCO_3^- excretion increase, with water free of electrolytes retention. To the best of our knowledge it was what happened to our patient.

A genetical study would confirm the diagnosis and clarify about additional anomalies but we didn't performe it because of economic issues. However, we still don't have many doubts about the diagnosis because there is a large phenotype variability without relationship between the clinical severity and type of mutations. Furthermore, heterozygotes have a higher rate of sodium excretion than wild-type individuals, probably due to higher salt intake.[10]

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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Afectación multigénica en el síndrome nefrótico congénito

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Sr. Director:

El síndrome nefrótico congénito (SNC) es una enfermedad grave y rara de herencia autosómica recesiva y monogénica en la mayoría de las ocasiones. Existen diferentes genes implicados, siendo los más frecuentes NPHS1, NPHS2, WT1 y LAMB2[1,2]. Clínicamente se manifiesta con proteinuria masiva, edemas generalizados, hipoalbuminemia e hipertrigliceridemia de aparición en los primeros tres meses de vida[3]. Presentamos el primer caso de un paciente afecto de SNC con alteración multigénica de tres de los cuatro genes más frecuentes.

CASO CLÍNICO

Se trata de un varón de un mes de vida, de origen marroquí, que acude a Urgencias por presentar vómitos, rechazo del alimento y distensión abdominal de 4 días de evolución. El embarazo fue controlado, sin existir antecedentes obstétricos ni perinatales de interés, naciendo a término y con un peso adecuado a su edad gestacional. En la exploración destacaba un regular estado general, con palidez cutáneo-mucosa y edemas generalizados de predominio en las extremidades inferiores. Se auscultó un soplo sistólico grado IV/VI polifocal. El abdomen estaba distendido, con presencia de red venosa superficial y ascitis. El examen de laboratorio mostró la presencia de anemia normocítica normocrómica, leucocitosis con fórmula normal, creatinina menor de 0,2 mg/dl y urea de 10 mg/dl, aumento del colesterol y los triglicéridos, y disminución de proteínas totales y albúmina, además de hiponatremia, hipopotasemia e hipocalcemia (tabla 1). La hormona paratiroidea se encontraba levemente elevada. En orina presentaba una proteinuria en rango nefrótico con índice proteinuria/creatinuria de 33,7.

Ante la sospecha de SNC, se inició terapia intensiva diurética y antiproteinúrica, profilaxis antitrombótica, tratamiento adyuvante con alfacalcidiol, hierro, carbonato cálcico y levotiroxina, además de nutrición enteral con fórmula hiperproteica e hipercalórica. Precisó tratamiento con seroalbúmina y eritropoyetina. En el estudio cardiológico se diagnosticó estenosis pulmonar valvular moderada y comunicación interauricular. En el estudio genético se encontraron las mutaciones tipo Frameshift para el gen NPHS1, tipo Intronic Variant para el gen NPHS2 y tipo Missense para el gen WT1.

A los tres meses de edad reingresó por presentar estatus convulsivo secundario a hipocalcemia grave. Debido a los aportes elevados de calcio intravenoso que precisó para su control a través de un acceso venoso periférico, se produjo una quemadura de tercer grado que necesitó la colocación de injerto cutáneo.

Precisó cuidados intensivos en dos ocasiones a los 4 y 6 meses de edad por sepsis secundaria a *Staphylococcus hominis* y *Enterococcus faecalis*, respectivamente, que se resolvieron con antibioterapia empírica y posteriormente según antibiograma.

Finalmente, el paciente falleció a los 8 meses de edad debido a una neumonía bilateral asociada a neumotórax con descompensación de su patología de base que provocó una hipoxemia refractaria.

DISCUSIÓN

El SNC puede sospecharse en el período prenatal por niveles elevados de alfafetoproteína, manteniendo cifras normales de colinesterasa a partir de la semana 15 de gestación en líquido amniótico y sangre materna[2,4]. En el nacimiento orienta la asociación de prematuridad y placenta grande[5], datos no presentes en nuestro paciente.

La causa más frecuente de esta entidad es la mutación del gen NPHS1, de herencia autosómica recesiva, y responsable de la codificación de la nefrina[2,5,6]. Esta alteración es particularmente común en Finlandia, por lo que se le ha dado el nombre de SNC de tipo finlandés. El gen NPHS2 codifica la proteína podocina y es la causa más común de corticorresistencia en la infancia[7]. Por otra parte, el gen WT1 juega un papel crucial en el desarrollo embrionario del riñón y los genitales, y se ha relacionado con la presentación de síndromes tales como el WAGR, Denys-Drash o