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**Clara Gómez-Pérez¹, Ane Mujika-López²,
Teresa Visus-Fernández de Manzanos²,
Eva Álvarez-Quintana²,
Francisco J. Gainza-de Los Ríos²,
Nerea Gómez-Larrambe²**

¹ Servicio de Hematología. Hospital Universitario de Cruces. Barakaldo, Vizcaya. (Spain).

² Servicio de Nefrología. Hospital Universitario de Cruces. Barakaldo, Vizcaya. (Spain).

Correspondencia: Ane Mujika López

Servicio de Nefrología.
Hospital Universitario de Cruces.
Barakaldo, Vizcaya. (Spain).
ane.mujikalopez@osakidetza.net
ane.mujikalopez@gmail.com

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 occasional muscle cramps. Water intake $\geq 3L$ /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 pointing 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 pCO_2 (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 useful in hyperkalemia

Table 1. Results of the laboratory investigation

	Patient values	Normal values
Complete blood count		
WBC ($\times 10^3/\mu\text{L}$)	7.30	4.0-10.0
Haemoglobin (g/dL)	15.60	12.0-16.0
Haematocrit (%)	44.90	36.0-46.0
Platelets ($\times 10^3/\mu\text{L}$)	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 ($\mu\text{mol/L}$)	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 ($\mu\text{mol/L}$)	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 ($\mu\text{g/dL}$)	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
pCO ₂ (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
PCO ₂ (mmHg)	46	35-48
PO ₂ (mmHg)	118	83-108
HCO ₃ (mEq/L)	35.90	22.0-31.0
O ₂ 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

settings. Additionally, 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 pCO₂ elevation increases renal acid excretion stimu-

lating renal ammoniogenesis, 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 secretion 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 HCO₃⁻ is being excreted. Adding to this, in severe hypokalemia, via unknown mechanism, distal chloride excretion is increased causing a parallel 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 HCO₃⁻ 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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Maria Guedes-Marques¹, Cirstina Silva¹, Emanuel Ferreira¹, Pedro Maia¹, Armando Carreira¹, Mário Campos²

¹ Servicio de Nefrología.
CHUC - Hospital dos Covões. Coimbra (Portugal).

² Servicio de Nefrología.
CHUC - HUC. Coimbra (Portugal).

Correspondence: Maria Guedes Marques
Servicio de Nefrología.
CHUC - Hospital dos Covões.
Quinta dos Vales - S. Martinho do Bispo,
3041-801 Coimbra (Portugal).
mariaguedesmarques@gmail.com

Multigene involvement in congenital nephrotic syndrome

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To the Editor,

Congenital nephrotic syndrome (CNS) is a serious, rare disease which in most cases has autosomal recessive monogenic inheritance. Several genes are implicated, the most frequent of which are NPHS1, NPHS2, WT1 and LAMB2.^{1,2} It manifests clinically with massive proteinuria, general oedema, hypoalbuminaemia and hypertriglyceridaemia appearing in the first three months of life.³ Here, we present the first case of a CNS patient with multigenic alteration of three of the four most common genes.

CASE REPORT

Our patient was a one-month-old male from Morocco, who came to the Emergency department after presenting symptoms such as vomiting, rejection of food and abdominal distension which had lasted 4 days. The pregnancy was controlled, with no relevant obstetric or perinatal history. The baby was born full-term with the proper weight for his gestational age. On examination the patient's general condition was fair, with cutaneous-mucous paleness and general oedema predominant in the lower limbs. A grade IV/VI polyfocal systolic murmur was auscultated. The abdomen was distended, with the presence of the superficial venous system and ascites. Laboratory analyses revealed normocytic-normochromic anaemia, leukocytosis with a normal formula, creatinine below 0.2mg/dl and 10mg/dl urea, high cholesterol and triglycerides, and reduced total proteins and albumin, as well as hyponatraemia, hypopotassaemia and hypocalcaemia (Table 1). The parathyroid hormone was slightly high. The patient's urine presented nephrotic-range proteinuria with a urine protein:creatinine index of 33.7.

When CNS was suspected, the patient began to undergo intensive diuretic and antiproteinuric therapy, antithrombotic prophylaxis, adjuvant treatment with alfacalcidol, iron, calcium carbonate and levothyroxin, as well as enteral nutrition with hyperprotein, hypercaloric formula. He required treatment with serum albumin and erythropoietin. Moderate pulmonary valve stenosis and atrial septal defect were diagnosed in the cardiology study. The genetic study revealed mutations of the frameshift type for the NPHS1 gene, of the intronic variant type for the NPHS2 gene and of the missense type for the WT1 gene.

At three months of age he was readmitted due to convulsive status epilepticus secondary to severe hypocalcaemia. The high quantities of intravenous calcium which needed treatment via peripheral venous access caused a third-degree burn which required a cutaneous graft to be placed.

Intensive care was required on two occasions, at 4 and 6 months of age, for sepsis secondary to *Staphylococcus hominis* and *Enterococcus faecalis* respectively, which were resolved with empirical antibiotic treatment and then according to the results of the antibiogram.

Finally, the patient died at 8 months of age due to bilateral pneumonia linked to pneumothorax with decompensation of the underlying pathology which caused refractory hypoxaemia.

DISCUSSION

CNS may be suspected in the prenatal period due to high levels of alpha-fetoprotein, maintaining normal figures for cholinesterase from the 15th week of gestation in amniotic fluid and maternal blood.^{2,4} At birth the link between premature birth and a large placenta can provide guidance,⁵ factors which were not present in our patient.

The most frequent cause of this condition is the NPHS1 gene mutation,