Gitelman's syndrome – a diagnosis to have in mind

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Abstract

Gitelman's syndrome, also referred to as familial hypokalaemia--hypomagnesaemia or benign variant of Bartter's syndrome, is an inherited renal tubular disorder transmitted with an autosomal recessive pattern.

Clinically it is characterized by hypokalaemia, metabolic alkalosis, hypomagnesaemia, hypocalciuria and secondary hyperaldosteronism.

A mutation in the SLC12A3 gene (Solute Carrier Family 12, Member 3 gene) encoding the thiazide-sensitive NaCl cotransporter (NCCT), is responsible for this syndrome.

Although a rare disease, the heterozygotes prevalence is about 1%, making it one of the most common hereditary renal tubular diseases.

Most cases are identified, by chance, during adolescence or in adulthood.

Weakness, paraesthesias, tetany and lower blood pressure than in the general population, respond well to supplements of the lacking salts and to potassium sparing diuretics, granting a long term prognosis, being our case an example.

Key words: Gitelman's syndrome, familial hypokalaemia-hypomagnesaemia, benign variant of Bartter's syndrome, SLC12A3, thiazide sensitive NaCl cotransporter, NCCT.

INTRODUCTION

The case is reported of a young woman with history of multiple hospitalizations for hypokalaemia, who abandoned follow-up at the Paediatric Nephrology, where she was being seen for a pathology she was not aware of. Family history included tubulopathy, which the patient could not specify.

Gitelman's syndrome is one of the most common hereditary tubulopathies; although it is accidentally diagnosed in most cases, and has an excellent prognosis, it is of interest to include this entity in the differential diagnosis of hypokalaemia, particularly in cases where there is family history of this pathology.

CLINICAL CASE

EFS, 21 years, female, of Gypsy ethnicity, single, a tradeswoman. Born and residing in Lisbon.

The patient had been hospitalized several times before for hypokalaemia and hypomagnesaemia of unclear etiology.

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The patient was followed-up at the Paediatric Nephrology department for a pathology diagnosed when she was 13 years old, but which she could not specify; she stopped showing up for the consultations, during which time she was randomly taking potassium and magnesium supplements.

Family history included tubulopathy, which the patient was also unable to specify, apparently without serious complications, diagnosed in two of her brothers, who were also in follow-up at the same clinic.

The patient visited the Emergency Department of Hospital de Santa Maria on the 27th July 2008 for a condition characterized by paresthesia of the hands, palpitations and anxiety, with several days of evolution and worsening three days before hospitalization.

On admission, the patient was anxious, with blood pressure of 128/78 mmHg, heart rate of 136 bpm, and ear temperature was 36.7ºc; no changes were observed on objective examination, except tachycardia.

Laboratory tests included hypokalaemia of 2.4 mEq/L and hypomagnesaemia of 1.2 mg/dL.

ECG was performed, revealing sinus tachycardia (ventricular response: 121 bpm), without changes suggestive of hypokalaemia.

Chest X-ray PA view did not show any changes.

The patient was admitted to the Medicine Service I for correction of the ionic disequilibrium and clarification of her condition.

During hospitalization, potassium and magne-

TABLE I

Laboratory changes

Parameter	Patient	Reference Values
Urine sodium	407 mmol/24 h	40-220
Urine potassium	108.3 mmol/24 h	25-125
Urine chloride	440 mmol/24 h	110-250
Urine calcium	224.2 mg/24 h	100-320
Urine magnesium	324.5 mg/24 h	60-210
Urine aldosterone	23.8 µg/ 24h	6-25
Serum aldosterone	209 pg/mL	10-160
Serum renin	42.1 pg/mL	1-20
Serum pH	7.472	7.35-7.45
Serum HCO3	28.7 mmol/L	22-26
Serum potassium	2.4 mEq/L	3.5-4.5
Serum magnesium	1.2 mg/dL	1.7-2.2
Serum chlorine	95 mmol/L	98-107

sium replacement was administered, and therapy with spironolactone was begun, which resulted in progressive correction of kalaemia and magnesemia, and remission of the condition.

On etiological investigation, urinary ionogram revealed: sodium 407 mmol/24 h (40-220), potassium 108.3 mmol/24 h (25-125), chlorides 440 mmol/24 h (110-250), calcium 224.2 mg/24 h (100-320), magnesium 324.5 mg/24 h (60-210). Urine aldosterone levels were 23.8 µg/24 h (6-25). Serum aldosterone levels were 209 pg/mL (10-160) and renin 42.1 pg/mL (1-20).

Arterial gasometry revealed pH of 7.472 (7.35-7.45) and HCO3 of 28.7 mmol/L (22-26), without any other changes.

Besides the ionic changes identified upon admission, hypochloraemia was 95 mmol/L (98-107), without changes in other ions, as shown in Table I.

During hospitalization, blood pressure remained low, ranging from 98-112/40-70 mmHg.

The practitioner, who had followed the patient on Paediatric Nephrology consultations, informed that the patient had Gitelman's syndrome, which was confirmed through a genetic assay. The patient was placed among a cohort of patients of Gypsy ethnicity with clinical suspicion of this pathology. A mutational analysis confirmed that the patient had specific homozygous mutations in the gene SLC12A3.[1]

The patient was discharged asymptomatic, with instructions to continue the potassium and magnesium supplements, and was referred to the Medicine clinic.

DISCUSSION

Due to of evidence of hypokalaemia with metabolic alkalosis, associated with high renin and aldosterone values, in a young woman with a tendency towards low blood pressure, the most consistent etiologies were anorexia nervosa or bulimia, use of diuretics, salt- and potassium-losing tubulopathies, namely Gitelman's and Bartter's syndromes.

Psychological pathologies that caused induced vomiting may include the occurrence of metabolic alkalosis and hypokalaemia due to loss of HCl in the gastric secretions, with a resulting volemic reduction.[2]

This reduction in volemic contraction leads to lower blood pressure, which induces the compensatory activation of the renin-angiotensin-aldosterone system (RAAS).

Nevertheless, the patient did not show signs of induced vomiting, such as ulcers, callus and scars on the backs of the hands, or tooth erosion due to the chronic exposure to HCl, which are almost pathognomonic of the abovementioned entities.[3]

The hyperchloruria observed in this case is also an element that allows us to safely rule out the presence of vomiting, since the elimination of chloride in the urine was invariably low in the last investigation (lower than 20 mEq/L).[2]

In the salt-losing tubulopathies, the loss of NaCl leads to a blood volume reduction with a consequent drop in the blood pressures, compensated by RAAS activation, which causes a state of secondary hyperaldosteronism, as was observed in this clinical case.[4]

The increase in the production of aldosterone promotes the excretion of K+ and H+ in the collecting ducts, causing hypokalaemia and metabolic alkalosis.

The mechanism of action of loop diuretics and thiazides mimics the abovementioned process,[5] however, the patient denied having taken these drugs.

The administration of laxatives can also interfere with these metabolic changes and low blood pressure,[6] nevertheless, in this case, there is no history of its use.

Because there was family history of apparently benign hereditary tubulopathy, and due to hypomagnesaemia, hypochloraemia and changes observed in the urinary ionogram, the patient was diagnosed with Gitelman's syndrome, which was subsequently confirmed by the paediatrician, who was armed with the results of the genetic assay and had followed up the patient's evolution.

For the first time, in 1966, Gitelman and colleagues described a salt-losing hereditary tubulopathy, characterized by hypochloraemic and hypokalaemic alkalosis, associated with hypomagnesaemia and hypocalciuria.[7-9]

Gitelman's syndrome has an autosomal recessive pattern, and is linked to inactivating mutations in the gene SLC12A3, which codes for the cotransporter of thiazide-sensitive NaCl located at the apical membrane of the distal convoluted tubule (DCT).[8-12]

An estimated prevalence of 1/40,000, in addition to a prevalence of heterozygote of around 1%, make this pathology one of the most common familial tubulopathies and a diagnosis to bear in mind.[7]

More than 140 mutations have been identified, which gives the pathology great genetic heterogenicity.[7,8] These mutations are simple, and characterized in most of the cases by the replacement of a single amino acid, but affect key elements in the tubular transport.[13]

Mutations in the gene CLCNKB have also been described; this gene codes for the chlorine CLC-Kb channel, in a small group of patients.[7]

This genetic diversity is translated by marked intra- and inter-familial phenotype variability and for the same mutation, varying widely in terms of age of onset, magnitude of the biochemical changes, and clinical manifestations.[8]

The normal urinary excretion of calcium observed in the patient does not rule out the diagnosis, rather, it confirms the large phenotype heterogeneity of this syndrome.[14]

Although it is possible to establish a prenatal diagnosis, this is of little interest, given the poor correlation between genotype and phenotype, and the benign evolution of this pathology.[2]

Heterozygous individuals excrete more NaCl[15] and have a lower incidence of high blood pressure, with an estimated reduced risk of 59% at 60 years of age and an average reduction in blood pressure of 6.3/3.4 mmHg.[16]

The heterozygous pattern also results in a higher sensitivity to loop diuretics and thiazides.[13]

Nevertheless, in the homozygous individuals, the response to loop diuretics is similar to that of the general population, but natriuresis potentiated by thiazides is lower than would be expected, since the thiazide-sensitive cotransporter of NaCl is afunctional.[17-19]

Although it is known that magnesium reabsorption occurs at the distal convoluted tubule, the mechanisms underlying hypomagnesaemia and hypocalciuria observed in this syndrome are not clear enough.[9]

It is speculated that the increased proximal reabsorption of sodium and calcium, and apoptosis of the DCT cells may explain this process.[9]

It is typically diagnosed during adolescence or adulthood following muscle-skeletal complaints, or accidentally, due to hypokalaemia, as in this case.[5,7,12]

Blood pressure levels lower than the expected in the general population are characteristic of this entity, as observed in the clinical case presented here.[7]

Extremely rare cases of fatal arrhythmias due to ionic disequilibrium have been documented.[7]

Table II lists the symptoms that are characteristic of this pathology and their prevalence.

The response to magnesium and potassium supplements, associated with potassium-sparing diuretics, such as spironolactone and amiloride, in doses higher than the usual, 300 mg and 40 mg per day, respectively, usually have excellent results.[5,7,20]

In addition to these measures, a high sodium and potassium diet is recommended.[6]

In the case of asymptomatic individuals, an annual follow-up is the norm, often without the need to begin therapy.[6]

Because it has a favorable course, Gitelman's syndrome is also known as the benign variant of Bartter's syndrome, which is another type of salt-losing tubulopathy, with which the former was confused before its genetic characterization in 1996.[5]

Bartter's syndrome is a genetically different tubulopathy, which causes defects in the transport of ions in the thick ascending limb of the loop of Henle.[5]

It is usually diagnosed at birth, occurring linked to mental impairment, growth delay and nephrocalcinosis, due to hypercalciuria, which may determine the development of chronic renal insufficiency.[5]

This syndrome also differs from the Gitelman's syndrome due to its deficient capacity for renal

TABLE II

Symptoms and their prevalence[24]

Symptoms	Prevalence (%)
Craving for salt	90
Cramps	84
Fatigue	82
Dizziness	80
Nocturia	80
Parestesia	78
Thirst	76
Muscle weakness	70
Polydipsia	64.6
Low blood pressure	62
Palpitations	62
Arthralgia	54
Muscular pain	52
Polyuria	50
Weakness	44.2
Presyncope	34
Obstipation	16
Abdominal pain	16
Tetany and spasms	11.7
Enuresis	11.9

concentration,[4] it does not occur with associated hypomagnesemia[5] and has high urinary excretion of prostaglandins (PGE2), due to an increase in the production of cyclooxygenase 2, through the activation of RAAS.[21]

Of the five existing types of Bartter's syndrome, type III is the most similar to the Gitelman's syndrome due to the intermediate clinical spectrum between both mentioned tubulopathies, because nephrocalcinosis may not occur, neither the exacerbated production of prostaglandins; and it occurs during adolescence.[22]

If in the other types of Bartter's syndrome a simple serum and urine ionogram allows the distinction from the Gitelman's syndrome, as it was the case here, in type III, the differential diagnosis is more difficult, often requiring genetic characterization.

In the case presented here, the genetic assay carried out during Paediatric Nephrology consultation confirmed the suspected Gitelman's syndrome.

Another hereditary tubulopathy that could raise doubts regarding the aetiology of the observed symptoms is Liddle's syndrome, in which hypokalaemia and metabolic alkalosis also occur; however, the Gitelman's syndrome is also characterized by high blood pressure and low serum renin and aldosterone levels.[23]

CONCLUSION

Gitelman's syndrome is the most common potassium- and magnesium-losing hereditary tubulopathy, with a high heterozygous prevalence. Although it is congenital, it is clinically manifested during adolescence or later, in adulthood.

The clinical spectrum varies from the absence of symptoms to extremely rare cases of fatal arrhythmias, with excellent response to therapy.

It is important to bear this pathology in mind in cases of chronic hypokalaemia and hypomagnesaemia without objective aetiology, particularly when there is a family history of the disease. ■

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