Asterixis as a rare manifestation of Gitelman syndrome. A case report

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Case Report

Internal Medicine

OPEN ACCESS

Background:
Gitelman syndrome is a rare inherited tubulopathy characterized by mutations affecting sodium chloride and magnesium transport in the distal nephron. With an estimated prevalence of 1 in 40,000, it usually presents asymptomatically or with mild symptoms such as fatigue and muscle cramps, but can progress to severe complications such as hypokalemic paralysis and life-threatening arrhythmias. Diagnosis is often made incidentally through blood tests that reveal chronic hypokalemia and hypomagnesemia.
This report details the case of a 35-year-old man with a history of type 2 diabetes and recent onset of symptoms such as asthenia and asterixis as the striking symptom. Initial testing revealed severe electrolyte imbalances such as hyponatremia, hypokalemia, and hypomagnesemia leading to hospitalization of our patient and suspicion of Gitelman syndrome. Liver pathology was ruled out. The patient was placed on electrolyte replacement therapy, but continued to suffer from hyponatremia.
Biochemical and clinical criteria confirmed Gitelman syndrome, which was treated with oral sodium chloride and spironolactone, resulting in normalization of electrolyte levels and resolution of symptoms, highlighting the disappearance of asterixis. The patient was subsequently discharged home with follow-up to the nephrology outpatient clinic. This case highlights the importance of recognizing the subtle manifestations of Gitelman syndrome and the need for ongoing follow-up to mitigate complications. Ultimately, Gitelman syndrome can significantly impact patients' quality of life, comparable to more commonly recognized chronic diseases. Regular follow-up in nephrology is crucial for effective treatment and prevention of long-term kidney damage.

Keywords: Gitelman syndrome, asterixis.

Gitelman syndrome is a salt-losing tubulopathy caused by mutation of genes encoding sodium chloride (NCCT) and magnesium transporters in the thiazide-sensitive segments of the distal nephron [1]. Also referred to as familial hypokalemia-hypomagnesemia, is an autosomal recessive tubulopathy that is characterized by hypomagnesemia, hypocalciuria and secondary hyperreninemic hyperaldosteronism, which is responsible for hypokalemia and metabolic alkalosis [2].
The prevalence of Gitelman syndrome is said to be around 1 in 40,000 people, although it is potentially more common among Asians. This suggests that at least 1% of the population is a heterozygous carrier. However, the exact prevalence of GS is unknown because most cases are thought to be asymptomatic or have nonspecifc clinical findings [3]. Gitelman syndrome is arguably the most frequent inherited tubulopathy [4].

Clinical symptoms of GS are wide-ranging, from asymptomatic to mild symptoms of fatigue, nocturia, muscle weakness, or muscle cramps, and severe symptoms, such as tetany, paralysis, rhabdomyolysis, or lethal arrhythmia. GS is usually diagnosed by chance blood test, without any clinical signs for GS in childhood, adolescence, or adulthood [5]. It is usually diagnosed in later childhood or early adulthood, though rarely the diagnosis is made in the neonatal period [6].

A case study of five GS patients revealed that laboratory findings played a significant role in diagnosis, with malaise being the only acknowledged clinical symptom. The mean potassium was 2.5 ± 0.5 mmol/l, and the serum magnesium value was 1.3 ± 0.3 mg/dl [7].

The complications of Gitelman syndrome include chondrocalcinosis and sclerochoroidal calcifications. Patients may also present with growth

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DOI 10.5281/zenodo.14048338

Criteria for suspecting a diagnosis of Gitelman Syndrome
• Chronic hypokalemia (<3.5 mmol/l) with inappropriate renal potassium wasting (spot potassium-creatinine ratio >2.0 mmol/ mmol [>18 mmol/g])
• Metabolic alkalosis
• Hypomagnesemia (<0.7 mmol/l [<1.70 mg/dl]) with inappropriate renal magnesium wasting (fractional excretion of magnesium >4%)
• Hypocalciuria (spot calcium-creatinine ratio <0.2 mmol/mmol [<0.07 mg/mg]) in adults
• High plasma renin activity or levels
• Fractional excretion of chloride > 0.5%
• Low or normal-low blood pressure
• Normal renal ultrasound
Features against a diagnosis of Gitelman Syndrome
• Use of thiazide diuretics or laxatives
• Family history of kidney disease transmitted in an autosomal dominant mode
• Absence of hypokalemia (unless renal failure); inconsistent hypokalemia in absence of substitutive therapy
• Absence of metabolic alkalosis (unless coexisting bicarbonate loss or acid gain)
• Low renin values
• Urine: low urinary potassium excretion (spot potassium-creatinine ratio <2.0 mmol/mmol [<18 mmol/g]); hypercalciuria
• Hypertension, manifestations of increased extracellular fluid volume
• Renal ultrasound: nephrocalcinosis, nephrolithiasis, unilateral kidneys, cystic kidneys
• Prenatal history of polyhydramnios, hyperechogenic kidneys
• Presentation before age 3 years
Criteria for establishing a diagnosis of Gitelman Syndrome
• Identification of biallelic inactivating mutations in SLC12A3

Table 1. Diagnostic criteria for Gitelman Syndrome according to KDIGO 2017 [4].

retardation, pubertal delay, and short stature, as well as hypokalemic rhabdomyolysis and QT prolongation, which may increase the risk of ventricular arrhythmias and even sudden death. In addition, patients with GS may present with glucose intolerance or insulin resistance, or both, secondary to chronic hypomagnesemia and hypokalemia. Reports suggest that GS may be associated with glomerular proteinuria due to glomerular basement membrane abnormalities. Chronic kidney disease may develop in patients with GS due to chronic hypokalemia, which is associated with tubulointerstitial nephritis, tubular vacuolization and cystic changes, or volume depletion and increased renin-angiotensin-aldosterone, which may contribute to renal damage and fibrosis. For all these reasons, patients with Gitelman Syndrome require close monitoring to detect these complications [4].

Quality of life in Gitelman syndrome is similar in range to that described for more "significant" diseases such as hypertension, diabetes, congestive heart failure, and coronary artery disease [8].

We present the case of a patient with Gitelman Syndrome who had asterixis as a clinical manifestation.

Case report

35-year-old male with a 2-year history of type 2 diabetes on metformin 850 mg 1 tablet every 12 hours. Positive alcoholism at a rate of 12 beers per week, converted to 12 grams of alcohol per week, suspended two months ago. A week ago, he began to have asthenia, hypodynamia and general malaise, so he went to a private hospital where the following laboratories were performed: complete blood count: hemoglobin 12.7 g/dL, hematocrit 38.1%, red blood cells 4.2 mill/mm3, MCV 91.1 Fl, HCM 30.3 Pg, white blood cells 14,630/mm3, lymphocytes 15%, segmented 75%, band neutrophils 0%, platelets 216,000/mm3, blood chemistry: glucose 302 mg/dL, BUN 21.3 mg/dL, urea 45.5 mg/dL, creatinine 0.9 mg/dL, serum electrolytes: hyponatremia of 110.8 mmol/L, hypokalemia of 3.02 mmol/L and hypochloremia of 86.2 mmol/L. The patient was sent to our hospital, however, in the emergency room, treatment was given for hydroelectrolytic imbalance and it was decided to discharge him home.

A month later, the patient returned to our unit due to somnolence, disorientation, asthenia, hypodynamia, dysarthria, asterixis of both upper limbs and generalized decrease in muscle strength for 5 days.

His vital signs on admission were as follows: heart rate of 90 beats per minute, respiratory rate of 25 breaths per minute, blood pressure of 111/79 mmHg, temperature of 36.5 degrees Celsius, and SatO2 of 98% without the use of supplemental oxygen. Physical examination revealed dry oral mucosa, hyporeflective pupils, asterixis and presence of a cogwheel sign of

DOI 10.5281/zenodo.14048338

upper limbs, muscle strength 4/5 on the Daniels scale in the upper and lower extremities, hyporeflexia in both lower extremities, as well as abdominal distension.

New laboratory tests were performed, revealing hyponatremia of 125 mmol/L, hypocalcemia of 6.9 mmol/L and hypomagnesemia of 0.8 mg/dL, Potassium, chloride and phosphorus within normal parameters 4.0 mmol/L, 103 mmol/L and 2.1 mg/dL respectively. However, in the laboratory tests performed during the previous hospitalization, hypokalemia was present. An upper abdominal ultrasound was also performed, which reported normal liver, gallbladder, portal vein and both kidneys.

Liver function tests were also performed with the following results: total protein 6.8 g/dL, albumin 4.3 g/dL, AST 32.0 U/L, ALT 21 U/L, LDH 200 U/L, alkaline phosphatase 69 U/L, GGT 21 U/L, total bilirubin 0.6 mg/dL, indirect bilirubin 0.5 mg/dL, direct bilirubin 0.0 mg/dL, globulin 2.5 g/dL. D-dimer, lipid profile, clotting times and urinalysis with normal results.

Intravenous hydroelectrolyte replacement was started including a bolus of 3% hypertonic solution and magnesium sulfate, however the patient continued to have hyponatremia with results of 116 mmol/L with chronic, severe, euvolemic hypoosmolar hyponatremia, and hypomagnesemia of 1.5 mg/dL.

A simple cranial tomography was performed, showing data suggestive of bilateral cerebral atrophy, calcified granulomas of 2 to 3 mm in both parietal lobes, without the presence of edema.

Arterial blood gas analysis was performed, showing metabolic alkalosis. A thyroid profile was also performed, with no alterations. Electrocardiogram without alterations. Urinary electrolytes were requested, with urinary Na values of 192 mEq/L, urinary K of 126.1 mEq/L, and urinary Cl of 91 mEq/L, and hypocalciuria with urinary Ca values of 16.7 mg/24 hours.

The patient met the biochemical criteria for the diagnosis of Gitelman syndrome, since he presented chronic hypokalemia during his last hospitalization of 3.02 mmol/L, with inappropriate renal loss of potassium, with a potassium-creatinine ratio greater than 2 mmol/mmol, metabolic alkalosis, hypomagnesemia of 0.8 mmol/L, hypocalciuria of 16.7, normal blood pressure of 111/79 mmHg, and a normal renal ultrasound [1, 2, 4].

The diagnosis of Gitelman Syndrome was made, and a 3% hypertonic solution infusion was started, however the patient continued to have hyponatremia of 128 mmol/L despite treatment, so it was decided to suspend the hypertonic solution infusion and start taking 3 g sodium chloride tablets orally every 8 hours and 25 mg spironolactone tablets orally every 12 hours. Latest electrolytes with Na of 136 mmol/L, potassium at 3.5 mmol/L, Cl of 111 mmol/L, Ca at 9.8 mg/dL, P at 5.1 mg/dL, and Mg at 1.9 mg/dL, In addition to presenting clinical improvement, highlighting the disappearance of asterixis, so it is decided to discharge him home with treatment with spironolactone 25 mg every 12 hours, sodium chloride tablets, 2 grams in the morning and 1 gram in the afternoon and at night and linagliptin for his type 2 diabetes. Instructions were also given to continue his follow-up in the nephrology outpatient clinic.

Discussion

Gitelman syndrome is an autosomal recessive tubular disorder caused by mutations of some of the genes encoding the sodium, chloride, and magnesium carriers in the apical membrane of the distal convoluted tubule, which is responsible for 7% to 10% of tubular absorption of electrolyte. Magnesium channels are also down-regulated in the duodenal cells. The mutations involve the SLC12A3 gene, which encodes the thiazide-sensitive sodium chloride cotransporter (NCCT), and the TRPM6 gene (Claudin 16 cation channel subfamily 6), which is responsible for distal tubular magnesium transport. The disease is a manifestation of an inactivating biallelic mutation in the SLC12A3 gene encoding the thiazide-sensitive sodium chloride cotransporter (NCC) present in the apical membrane of distal convoluted tubule cells [1]. Greater than 350 mutations have been reported [9]. Most patients are heterozygous for SLC12A3 mutations, but many patients with GS have been found to have only a single SLC12A3 mutation [1].

The diagnosis of Gitelman syndrome is based on the clinical symptoms and biochemical abnormalities. The most typical biochemical abnormalities in GS are hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria [2].

Diagnostic criteria according to the 2017 KDIGO consensus are listed in Table 1 [4].

Our patient with the only relevant history of type 2 diabetes of two years' evolution, presented chronic hypokalemia on admission of 3.02, metabolic alkalosis with pH of 7.52, HCO3 of 28, pCO2 of 36, hypomagnesemia of 0.8 mg/dL which converted to mmol/L is 0.3 mmol/L, hypocalciuria of 16.7 mg/24 hours, blood pressure within normal parameters and normal bilateral renal ultrasound. In addition to a clinical picture compatible with drowsiness, disorientation, asthenia, hypodynamia, dysarthria, decreased muscle strength in all four extremities and most strikingly asterixis of both upper limbs. All this compatible with the diagnosis of distal convoluted tubulopathy specifically with the clinical and biochemical diagnosis of Gitelman Syndrome.

DOI 10.5281/zenodo.14048338

Barter syndrome was ruled out because our patient's urinary calcium was not within normal or increased ranges, but rather he had hypocalciuria characteristic of Gitelman Syndrome [9, 10].

A thyroid profile, D-dimer, and lipid profile were performed with no alterations. Liver function tests and an upper abdominal ultrasound were also performed with no alterations, ruling out a hepatic origin of these symptoms.

Regarding the treatment of Gitelman Syndrome, which is caused by a primary defect in a sodium chloride cotransporter, the intake of NaCl "ad libitum" should be strongly recommended. As yet, the potential benefit of pharmacological NaCl supplements added to liberal salt intake has not been tested [4].

Individualized lifelong oral potassium or magnesium supplementation or both is the mainstay of treatment for patients with GS. Many symptoms are improved by potassium or magnesium supplementation or both, but there is no evidence correlating the severity of blood levels with the intensity of symptoms. A reasonable target for potassium may be 3.0 mmol/l and magnesium 0.6 mmol/l (1.46 mg/dl). Potassium supplements should be given as chloride, because chloride is the main anion lost in the urine and patients are alkalotic [4].

Oral administration of magnesium supplements is the preferred way to correct magnesium deficiency, which aggravates hypokalemia and renders it refractory to treatment by potassium. All types of magnesium salts are effective, but their bioavailability is highly variable [4].

In cases of persistent and symptomatic hypokalemia, when supplementation is not sufficient despite adherence or when side effects are unacceptable or both, potassium-sparing diuretics, renin-angiotensin system blockers or nonsteroidal anti-inflammatory drugs, such as indomethacin, or a combination of them, can be used [4]. Each has its characteristic side effects that we will not discuss in this article.

The treatment of our patient at the beginning was with hydroelectrolyte replacement with infusion of 3% hypertonic saline solution and magnesium sulfate, closely monitoring the serum electrolyte values, hypomagnesemia was resolved, however, hyponatremia continued refractory to treatment, the infusion was suspended and sodium chloride tablets 3 gr orally every 8 hours and spironolactone tablets 25 mg orally every 12 hours were added. After this the blood electrolyte values normalized, the symptoms improved and the asterixis characteristic of this case disappeared.

Conclusion

Gitelman syndrome is a rare autosomal recessive tubulopathy that is most often diagnosed in childhood, adolescence, or adulthood. It is usually diagnosed by a random blood test, without clinical signs, although patients may have symptoms at the time of diagnosis. Most diagnoses are incidentalomas so it is believed to be underdiagnosed. Due to its rarity and variability in symptomatology, the diagnosis of Gitelman syndrome is often challenging, so high clinical suspicion is required by physicians.

There is not cure for Gitelman syndrome, however it requires lifelong treatment with potassium and magnesium supplements, in addition to unrestricted sodium intake. In some cases when hypokalemia persists despite supplementation, other types of medications such as potassium-sparing diuretics, renin-angiotensin system blockers, or nonsteroidal anti-inflammatory drugs, such as indomethacin, may be added. In addition, these patients require close monitoring by a nephrologist and nutritionist because they require changes in their diet, such as a diet rich in potassium and magnesium.

Conflicts of interests

The authors declare no conflicts of interests.

Acknowledgements

We thank our patient and her mother for allowing us to use their case in this publication.

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 DOI 10.5281/zenodo.14048338