# GITELMAN SYNDORME - THE IMPORTANCE OF IONOGRAM AND BLOOD GASES IN DIAGNOSIS

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**Abstract**

Aim: To present a case with severe hypopotassemia, hypomagnesemia, hypocalcemia, hypocalciuria and metabolic alkalosis. Material: A 14 years old male patient was admitted for carpopedal spasm, muscle weakness, facial and upper limbs paresthesia, with diminished left<right muscle tone. In the past, he presented 3 similar episodes of carpopedal spasm, vomiting and diarrhea with hydroelectrolytic disturbances which were considered due to gastroenterocolitis and treated therefore. Results: Laboratory tests detected metabolic alkalosis, severe hypokalemia, hypomagnesemia, hypocalcemia and hypocalciuria. It was initiated the replacement treatment of electrolytes with a partial correction. Regarding the medical history, the present symtomatology, the difficult correction and after the exclusion of other causes of unexplained severe hypokalemia, hypomagnesemia and metabolic alkalosis, diagnosis of Gitelman Syndrome was established, confirmed by genetic test. Lifelong daily supplementation with magnesium and potassium was recommended. Conclusion: For an accurate diagnosis it is essential to interpret correctly both the symptoms and the laboratory tests (ionogram, blood gases) so as further consequences would be excluded.

**Keywords:** ionogram, blood gases, tubulopathy

**Introduction**

Gitelman Syndrome is an autosomal recessive disorder with metabolic abnormalities. It is also called tubular hypomagnesemia-hypokalemia and the difference between Bartter Syndrome is the absence of hipercalciuria [1,2]. The characteristic sets of metabolic abnormalities include: hypokalemia, metabolic alkalosis, secondary hyperaldosteronism with hyperreninemia, and sometimes hypomagnesemia [3].

The prevalence of Gitelman Syndrome has been estimated to be between 1 to 10 in 40,000 compared with Barrter syndrome 1 in 1,000.000, therefore it is more frequent [4,5]. Usually it is diagnosed in late childhood or adulthood in contrast to the typical neonatal clinical presentation of Barrter Syndrome [6].

Gitelman syndrome is caused by biallelic inactivating mutations in the SLC12A3 gene encoding the thiazide-sensitive sodium-chloride cotransporter (NCC) expressed in the apical membrane of cells lining the distal convoluted tubule [7]. The symptoms that appear are similar to that seen with chronic use of a thiazide diuretic [8].

The clinical manifestations are: almost 10 percent of patients present at diagnosis with tetany, cramps of the arms and legs due to hypokalemia and hypomagnesemia. Fatigue may be seen, also poliuria, rarely growth retardation and later on hipertension. In general, these symptoms are associated with other manifestations so often the delay of diagnosis occurs [9].

The tubular defect in Gitelman Syndrome cannot be corrected, thus, treatment focuses on the correction of the electrolytes abnormalities with sodium, potasium and magnesium supplements as well as correcting the volume deficit [10].

**Aim**

To present a case with severe hypopotassemia, hypomagnesemia, hypocalcemia, hypocalciuria and metabolic alkalosis.

**Case report**

The 14 years-old boy was admitted to our clinic for carpal spasms and left hand paresthesia, with motor deficit on the same part, no other associated symptoms were reported. The symptoms appeared suddenly, during the night, while the patient was sleeping, determining him to wake up. In the morning, he referred to regional hospital, where the patient was evaluated. Blood tests showed hydro electrolytic disorders (pH=7.5, K= 2.4 mmol/l, Ca= 3,8 mg/dl) and elevated inflammation markers (CRP 45 mg/l). Because of the suspicion of encephalitis, a CT scan was also taken, without revealing any abnormal aspects. From that moment on, the patient was transferred to our hospital.

A physical examination at admission in our clinic revealed a moderate influenced general condition, fatigability, with elevated body temperature (37.8 Celsius degrees), normal colored skin, without any eruptive elements, moderate pharyngeal congestion, no palpable peripheral lymphadenopathy.

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Also, the pulmonary, cardiovascular, digestive and renal systems examination were normal, the value of blood pressure was 118/68 mmHg. Carpal spasms and paresthesia of the left hand were present, with a negative Chvostek sign.

Personal and disease history: he is the first-born child in the family, from a controlled full-term pregnancy, with no history of drugs use or exposure to radiation. Delivery was completed in the regional hospital.

He had several hospitalizations in the regional hospital. The first one occurred when he was 11-year old due to tetany in which carpal spasms predominated and gastroenterocolitis. The other two hospital admissions were usually for the same signs. In each hospitalization, the symptomatology was thought to be because of gastroenterocolitis which led to disturbances in fluid and electrolyte homeostasis. Each time, the patient was treated with intravenous infusions of electrolytes and fluids and then went at home, without further follow-up visits.

Blood tests showed metabolic alkalosis Ph of 7.49 (NR 7.35 to 7.45 HCO3-act of 31.9 mmHg (NR 21 to 26 mmHg), HCO3-std of 30.3 mmHg (NR 24 to 28 mmHg), BE of 7.4 (NR -2.5 to 5), hypocalcemia, ionized Ca of 1.01 mmol/L (NR 1.15 to 1.35 mmol/L), very low serum potassium of 2.04 mmol/L (NR 3.6 to 4.8 mmol/L), normal sodium concentration Na of 138.9 mmol/L (NR 135 to 145 mmol/L), hypomagnesemia Mg of 0.6 mmol/L (NR 0.7 to 1.05 mmol/L), and hypochloremia Cl of 94 mmol/L (NR 95 to 105 mmol/L). Other significant results included leukocytosis WBC of 19.89 x10^3/ul (NR 4.8 to 10.8 x 10^3/ul) with neutrophilia 15.78x 10^3/ul/ 79.6% (NR 1.87 to 8.1 x10^3/ul/ 39 to 70%), normal hemoglobin 12.8 g/dL (NR 11.8 to 15.7 g/dL) and elevated inflammation markers CRP of 57.46 mg/L (NR 0 to 5 mg/L). His serum aminotransferases, glycemia, urea, and creatinine levels were normal. Urine/24h has been collected and revealed loss in potassium :128 mmol/24h (NR 35 to 80 mmol/24h) and hypocalciuria: urine Ca of 0.65 mmol/24h (NR 1.75 to 7.5 mmol/24h). Renin and aldosterone were normal in our case. Echocardiography showed no pathological aspect.

**Discussion**

Hypopotassemia caused by vomiting, diarrhea or due to different drugs (especially diuretics) abuse were excluded. Also, because of the normal range of aldosterone and renin, there is no point in suspicioning a Liddle Syndrome, a primary hyperaldosteronism or a renin secreting tumors. Other diseases were excluded: Fanconi Syndrome (proteinuria, glycosuria, hypercalciura, nephrocalcinosis), type 1 tubular acidosis (metabolic acidosis, hypopotassemia, hypocloremia). The main differential diagnosis is made with Bartter Syndrome (especially type III, caused by mutation in CLCNKB); the two syndromes can be clinically indistinguishable, but there are some features like the age of the patient (14 years old with normal development in our case, in contrast with Bartter Syndrome, where children are symptomatic since neonatal period or early childhood and have failure in growth).

Genetic tests were performed that showed mutations in the SLC12A3 gene that encodes the thiazide-sensitive sodium-chloride cotransporter (NCC), fact that confirms our suspicion of diagnosis - Gitelman Syndrome.

Because of the severe hypopotassemia, the treatment was urgent. It was administrated potassium intravenous 40mmol/l through peripheral vein with the rythm of 10mmol/h, because greater concentrations may lead to venous sclerosis and magnesium sulphate intravenous, all this time the patient being cardiac monitored. Despite the agressive treatment, the potassium concentration still didn't achieve normal range. Moreover, the next day, the patient started to acuse heart palpitations and we opted the next three days for substitutive oral treatment, with potassium chloride oral 50 ml, magnesium orotate and gluconate calcium. Only after those three days of treatment, the potassium reached the targeted range of over 3.00 mmol/L ( 3.09 mmol/L) (Fig. 1). The magnessium levels were still below the normal range ( Mg of 0.61 mmol/L) (Fig. 2).

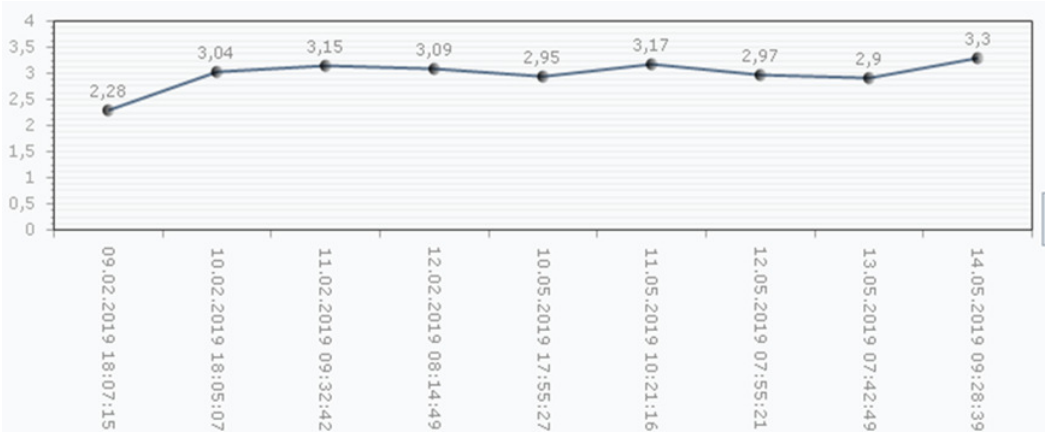


Fig 1. Potassium levels during the admittance.

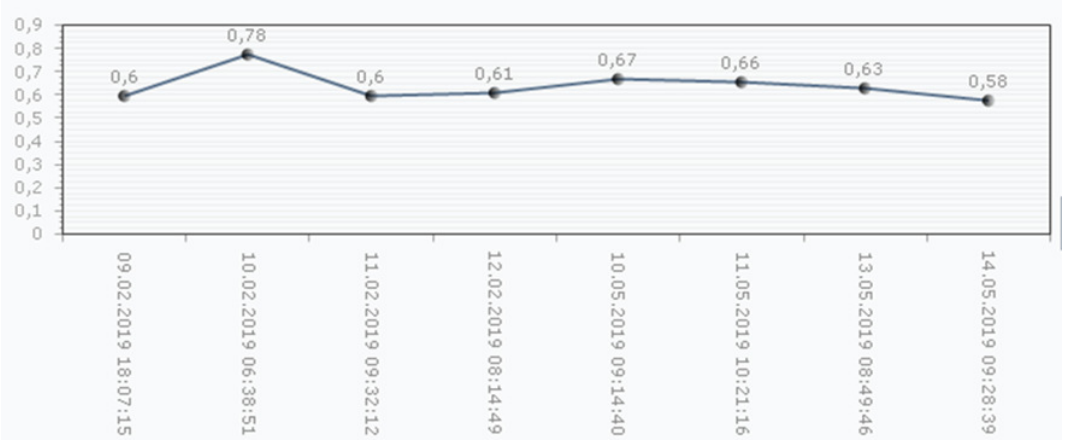


Fig. 2 Magnesium levels during the admittance.

Clinically, the patient had a good general condition, without any other sympthomatology. At home oral substitutive treatment, with magnesium orotate, lactic calcium and potassium and magnesium supplement (Aspacardin) for long term and nonsteroidal anti-inflammatory drugs (Indomethacin) oral 50mg/day for seven days were prescribed.

Individualized lifelong oral potassium or magnesium supplementation or both is the mainstay of treatment for patients with Gitelman syndrome. The KDIGO guidelines recommend a target K of 3 mmol/l and a target Mg of 0.6 mmol/l in patients with Gitelman syndrome [11]. In the presence of hypomagnesemia, magnesium supplementation should be considered first, because magnesium repletion will facilitate potassium repletion and reduce the risk of tetany and other complications. Intravenous KCl may be necessary either when the patient cannot take oral drugs or when the potassium deficit is very severe, causing cardiac arrhythmias, quadriplegia, respiratory failure, or rhabdomyolysis.Also, a series of drugs should be avoided or used with caution (table 1) and a diet rich in magnesium and potassium is recommended [12,13].

Table 1 Drugs associated with hypokalemia and hypomagnesemia.

| Site of loss | Drugs |
|---|---|
| **Hypokalemia** | |
| Shift from extracellular fluid to intracellular fluid compartment | $\beta_2$-receptor agonists<br>Insulin (high dose) with glucose<br>Xanthines (theophylline, caffeine)<br>Verapamil (in overdose)<br>Sodium bicarbonate |
| Extrarenal | Laxatives |
| **Renal** | |
| Antimicrobials | Nafcillin, ampicillin, penicillin, aminoglycosides, amphotericin B, foscarnet |
| Diuretics | Acetazolamide<br>Furosemide and other loop diuretics<br>Thiazides<br>Mannitol |
| Mineralocorticoids | Fludrocortisone |
| Antiepileptic | Topiramate |

| Site of loss | Drugs |
|---|---|
| **Hypomagnesemia** | |
| Extrarenal | Proton pump inhibitor |
| **Renal** | |
| Antimicrobials | Drug-induced renal Fanconi syndrome: Aminoglycosides (gentamycin, streptomycin, tobramycin), pentamidine, amphotericin B, foscarnet, antiretroviral therapy |
| Diuretics | Furosemide<br>Thiazide |
| Antitumoral | Cisplatin<br>Tyrosine kinase inhibitors |
| Immunosuppressants | Calcineurin inhibitors (cyclosporine, tacrolimus)<br>Mycophenolate<br>Anti-EGF receptors (cetuximab, panitumumab) |

Long-term studies are needed to assess the natural history of GS and the individual risks of chronic hypokalemia and hypomagnesemia in terms of metabolic syndrome, cardiac arrhythmias, chronic kidney disease, blood pressure control, and propensity to develop chondrocalcinosis. To date, there is no evidence that GS affects life expectancy [14]. Caution should be taken when patients with GS undergo anesthesia. Hypokalemia and hypomagnesemia can potentiate the effects of local and general anesthetic agents [15].

The patient returned for monthly follow-up visits. After three months, he accused again fatigability, carpal spasms and muscle awareness. At admission, the potassium and magnesium levels were low, but the patient and the parents admitted that the boy didn't took the medication at home for a few days. He was administrated potassium intravenous and as a result the electrolytes reached normal range, from what we understand the importance of the continuous treatment and individualized, with appropriate change with time and demands.

**Conclusions**

The purpose of our article is to remind us that the diagnosis of Gitelman Syndrome can be taken into consideration when we are in front of an unexplained hypokalemia, hypomagnesemia and metabolic alkalosis. For an accurate diagnosis it is essential to interpret correctly both the symptoms and the laboratory tests (ionogram, blood gases).

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