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Rare Presentation of Gitelman Syndrome: A Case Report

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ABSTRACT

Gitelman Syndrome (GS), also known as familial hypokalemia-hypomagnesemia, is a rare genetic disorder. GS presents with a specific defect in kidney function, that leads to hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria. Here, we present a 30-year-old woman without a medical history. She experienced an episode of tonic-clonic seizure, generalized muscle weakness, and severe hyponatremia as the first presentation of GS. The interesting point of this case was her late-onset presentation and the long period of her disease diagnosis; thus, it highlights the importance of considering this diagnosis.

Introduction

Gitelman's Syndrome (GS), also called the Gitelman's variant of Bartter's Syndrome (BS) is an inherited autosomal-recessive, salt-losing tubulopathy. GS is characterized by hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria [1]. The prevalence of GS is 1:40000 and presumably higher in the Asian population; it may be the most common inherited tubulopathy [2]. It is also known as the "milder" form of BS since patients with GS are usually detected during adolescence and in early childhood [3].

Phenotypic similarities exist among BS and GS; however, the presence of hypocalciuria and hypomagnesemia in GS is a distinguishing factor. Hypocalciuria is highly variable and hypomagnesemia may be absent [4].

It is caused by inactivating mutations in gene SLC12A3 on chromosome 16; it encodes for thiazide-sensitive sodium-chloride cotransporter and magnesium trans-

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porter on the apical membrane of the Distal Convoluted Tubule (DCT) [5]. GS is a benign tubulopathy and the condition may be asymptomatic. However, the symptoms reported by literature range from mild weakness, fatigue, salt craving, thirst, and nocturia to muscle weakness, rhabdomyolysis, paralysis, paresthesias, or the signs of neuromuscular excitability, such as tetany, and rare seizures [3, 6-8].

Case Presentation

The subject is a 30-year-old patient without a medical history. She experienced an episode of tonic-clonic seizure, generalized muscle weakness, and severe hyponatremia as the first presentation of GS. She was admitted to the hospital without a history of any illness. She was admitted to another hospital with epigastric pain, nausea, vomiting, weakness, lethargy, and weight loss of about 15 kg a month earlier. Biochemical analysis data suggested hypokalemia (2.6 mmol/L) and hyponatremia (132 mmol/L). Serum creatinine (0.8 mg/dL), and urea (10 mg/dL) were normal. Abdominopelvic ultrasound revealed no abnormality. EGD showed several erosions in antrum. she presented several erosions in her antrum. The patient was discharged with the diagnosis of anxiety disorder and gastritis and was treated for helicobacter pylori. A day after the discharge, she was referred to another clinical center with generalized tonic-clonic seizure and severe hyponatremia (serum sodium: 116 mmol/L). After primary stabilization of her situation, she left that hospital with personal consent.

One week later, again she was referred to another hospital with the symptoms of muscle weakness, urinary disturbances (burning sensation & frequent urination), and decreased DTR. The relevant laboratory evaluations indicated metabolic alkalosis (PCO2=34.1 mmHg, PH=7.558, HCO3=30.4 mmol/L), electrolyte disturbances; hyponatremia (125 meq/L), hypomagnesia (1.3 mg/dL), hypokalemia (2.8 meq/L), and urinary tract infection. Due to muscle symptoms, EMG/NCV was conducted; however, she manifested no evidence of myopathic disorders. Ultimately, the patient was discharged after rectifying electrolyte disturbances and was recommended to visit nephrology and neurology clinics.

Two weeks later, she was admitted with proximal muscle weaknesses (4/5 strength, symmetric), muscle cramps, polydipsia, and weight loss to our center. Initial laboratory experiments revealed hypokalemia (2.9 mmol/L) and hypomagnesia (1.4 mg/dL) despite oral magnesium consumption; metabolic alkalosis (PH=7.49, pCO_2=34.1 mmHg, HCO_3=26.5 mmol/L); disturbed random urine electrolyte (specific gravity=1015, Na=44 meq/L, K=15 meq/L, & Ca=14 meq/L). Her blood pressure was equal to 90/60 mm/Hg and had a regular pulse frequency of 80/min. EKG exhibited normal sinus rhythm and no clear abnormality.

Regarding the patient neuromuscular symptoms, a brain Magnetic Resonance Imaging (MRI) and neurology consultant were requested. Brain MRI result was normal, but EMG-NCV indicated chronic myopathic disorder in proximal muscles. Further investigations revealed normal levels of CPK, LDH, aldolase, and ESR. Serum cortisol level was in a healthy range (cortisol=19 & ACTH=12). The uric acid level was measured as 5.8 mg/dL. CBC, LFT, and TFT tests data were normal. Potassium, magnesium, calcium, and sodium urine levels were obtained as 50 mEq/L, 84 mEq/L, 168 mEq/L, and 78 mEq/L, respectively. A high level of plasma rein activity was observed in our patient (8 ng/mL/h). Considering the above-mentioned evidence and the probability of GS, the patient was treated with magnesium, potassium, and Non-steroidal Anti-inflammatory Drug (NSAID) supplements. Electrolyte disturbances were controlled, alkalosis was resolved, and muscle weakness was greatly improved. Eventually, the patient discharged with PH=7.35, K=5.2 mEq/L, mg=2.5 mg/dL, HCO3=25 mEq/L, and referred to nephrology clinic.

According to this evidence, a GS diagnosis was established for the patient. Accordingly, she was discharged with indomethacin, spironolactone, oral potassium, and magnesium prescriptions.

Discussion

GS, also known as familial hypokalemia-hypomagnesemia, is a salt-losing tubulopathy. GS is characterized by hypokalemic metabolic alkalosis, hypomagnesemia, and hypocalciuria. GS is caused by autosomal recessive mutations in the gene that encodes the Na^+-Cl– cotransporter (NCCT) that site of action of thiazide diuretics; thus, the laboratory features of GS are similar to a patient who is on thiazides [9]. These abnormalities lead to high levels of renin-angiotensin-aldosterone system activation and the over-secretion of PGE_2 and the suppression of both systems is a part of treatment [10].

This condition may be asymptomatic or associated with relatively mild or nonspecific symptoms, such as muscular weakness, fatigue, salt craving, thirst, nocturia, or cramps. However, this view has been challenged by reports emphasizing the phenotypic variability and potential severity of the disease.

Table 1. Criterias of suspecting diagnosis of GS

Criteria	Patient's Data
Chronic hypokalemia (<3.5 mmol/L) with inappropriate renal potassium wasting (spot potassium-creatinine ratio >2.0 mmol/mmol (>18 mmol/g)	Patient was hypokalemic (3 meq/L) And potassium was 15 meq/L in random urine and 50 meq in 24 houres urine
Hypomagnesemia (<0.7 mmol/L; <1.70 mg/dL) with inappropriate renal magnesium wasting (the fractional excretion of magnesium >4%)	Patient was hypomagnesimic And magnesium was 84 meq in 24 hours urine
Hypocalciuria (spot calcium-creatinine ratio <0.2 mmol/mmol; <0.07 mg/mg) in adults.	Patient was normocalcemic
High plasma renin activity or levels	Plasma renin activity was 8 ng/mL/hr
The fractional excretion of chloride >0.5%	-
Low or normal-low blood pressure	Patient blood pressure was 90/60 mmHg
Normal renal ultrasound	Normal ultrasound and abdominopelvic ct

Previous research studies indicated that GS is not an asymptomatic syndrome; GS patients were significantly more symptomatic than the controls. The most frequent symptoms were salt craving (90%) with musculoskeletal symptoms, such as cramps (84%), muscle weakness (70%), aches and constitutional symptoms, like fatigue (82%), generalized weakness and dizziness (44.2%), nocturia (80%), and polydipsia (64.6%) [11]. As per a study, 6% of patients were presented with muscle paralysis at the time of diagnosis. Besides, 3% of the explored patients reported at least one-lifetime history of seizure; however, according to their information, it presented no direct relationship with the disease [1].

In some cases, severe rhabdomyolysis and paralysis mimicking Guillen barre syndrome were described [12]. Manifestations, such as early-onset (before the age of 6 years), growth retardation, chondrocalcinosis, tetany, rhabdomyolysis, seizures, and ventricular arrhythmia have also been described In this respect [6, 7, 13-15].

In our patient, hypokalemia, hypomagnesemia, and metabolic alkalosis placed BS, GS, and superstitious use of diuretics, on top of our list of differential diagnoses. Our patient had no history of diuretic use. In further workup, she presented hypocalciuria and a high fractional exertion of magnesium in urine, i.e. in favor of GS diagnosis.

The main pathology of BS is a furosemide-receptor disorder, compared to GS, i.e. a thiazide-receptor defect. Thus, hypomagnesemia and hypocalciuria are distinct characteristics of GS. Although in GS patients, hypomagnesemia may be absent and hypocalciuria is variable.

The hydrochlorothiazide test can play a role in differentiating between GS and BS; however, it is no longer recommended. This is because GS has a diverse phenotypical variety and some patients may encounter a concurrent defect in the loop of Henle and are at risk of volume depletion. It has been proposed that biochemical criteria for clinically-diagnosing a GS [3]. The table below demonstrates that all the biochemical properties are compatible with the criteria.

The main presenting symptoms of our patient were an episode of tonic-clonic seizure, hyponatremia, as well as the manifestations of the chronic myopathic disorder. All of her symptoms were interpretable in the context of electrolyte imbalance of GS; however, other causes, like Thyrotoxic Periodic Paralysis (THPP) and Addison disease should have been considered. THPP is a rare metabolic myopathy that presents with acute systemic muscle weakness associated with hypokalemia, and potential fatal episodes of muscle weakness or paralysis that can affect the respiratory muscles [16].

Considering the paralysis and medical history of raised serum levels of CPK and the evidence of chronic myopathy in EMG-NCV, the THPP was in differential diagnosis; however, the patient manifested no sign of thyrotoxicosis and her TSH was in normal limits [7]. Addison rarely presents with metabolic alkalosis and hypokalemia; however, the ACTH and cortisol levels were within healthy limits and ruled out [17].

By ruling out other possible causes, evidence indicated the high probability of the GS although genetic testing is required for its confirmation; the unavailability and high

costs make the clinical criteria desirable in countries with lower economic power.

GS is usually treated by life-long administration of oral potassium and magnesium supplements and recommending to use a rich salt food regimen. Angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers are also generally advised. This is because they decrease potassium secretion in urine and suppress the high level of renin and aldosterone. NSAIDs were formerly used for BS patients; they have higher levels of PGE_2, but the phenotypical overlap between GS and BS makes them suitable for therapeutic management [3, 18].

Conclusion

We presented a 30-year-old woman without a medical history. She experienced an episode of tonic-clonic seizure, generalized muscle weakness, and severe hyponatremia as the first presentation of GS. The interesting point of this case was her late-onset presentation and the long period of her disease diagnosis; thus, it highlights the importance of considering this diagnosis.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed about the purpose of the research and its implementation stages.

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Conflict of interest

The authors declared no conflicts of interest.

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