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Gitelman syndrome presenting with lower limb paralysis: a case report

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Abstract

Background Gitelman syndrome is a rare autosomal recessive disorder that affects the distal convoluted tubules of the kidneys. It often manifests through various symptoms, including muscle weakness, paresthesia, fatigue, or paralysis. Owing to the scarcity of case reports regarding Gitelman syndrome in the Middle East and North Africa region, it is imperative to spread awareness about this syndrome for prompt diagnosis. Consequently, this could drastically decrease the rate of complications and help with its management and prognosis. This case report addresses the lack of awareness surrounding the syndrome. In addition to its unfamiliarity, the patient presented in this case exhibited hypokalemic periodic paralysis, which is a rare presentation of Gitelman syndrome.

Case summary A 17-year-old Egyptian male patient presented to the emergency department complaining of progressive lower limb weakness during the previous week. The patient had recurrent, brief episodes of lower limb paralysis for more than 2 years. Clinical examination revealed severe lower limb weakness with a power of 0/5 bilaterally. There was no evidence of upper limb or respiratory muscle involvement. Further investigations revealed severe hypokalemia, hypomagnesemia, metabolic alkalosis, hypocalciuria, and hyperreninemia. A positive family history, along with the aforementioned laboratory results, supported the diagnosis of Gitelman syndrome. The patient was then transferred to the high-dependency care unit, where aggressive correction of hypokalemia and hypomagnesemia commenced. With the resolution of the lower limb weakness, the patient was discharged home in a stable condition.

Conclusion Clinical history and biochemical findings helped in expediting the final diagnosis of Gitelman syndrome. With prompt electrolyte repletion, the patient regained full function and sensation in his lower limbs. Owing to the limited number of reported Gitelman syndrome cases within the Middle East and North Africa region, it is critical to increase exposure and knowledge of Gitelman syndrome.

Keywords Case report, Gitelman syndrome, Hypokalemia, Hypokalemic periodic paralysis, Hypomagnesemia

Introduction

Gitelman syndrome (GS), otherwise known as familial hypokalemia-hypomagnesemia, is a renal tubulopathy that often manifests with hypokalemia, hypomagnesemia, hypochloremia, metabolic alkalosis, and hypocalciuria [1]. Hypocalciuria is most frequently considered the factor that distinguishes it from Bartter syndrome, which conversely presents with hypercalciuria [2].

Gitelman syndrome has a genetic etiology with an autosomal recessive mode of inheritance [3]. In most

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cases, it is proven to be a result of an inactivating mutation affecting both alleles of the *SLC12A3* gene [4]. This, in turn, affects the function of the thiazide-sensitive sodium-chloride cotransporter found in the distal convoluted tubules of the kidneys [5]. These mutations may cause patients to be asymptomatic or to present with signs and symptoms that are nonspecific and mild. It may even mimic the signs and symptoms of patients on thiazide diuretics [6]. These can include polydipsia, salt cravings, low blood pressure, muscle cramps, fatigue, paresthesia, periodic paralysis, and palpitations [7].

The incidence of GS cases remains unreported within the Middle East and North Africa (MENA) region. With insufficient awareness of GS within this region, its diagnosis can be challenging and delayed. In this study, we report a case of GS in a 17-year-old Egyptian male patient who was diagnosed and treated in the United Arab Emirates.

Case presentation

A 17-year-old Egyptian male patient presented to the emergency department (ED) of our hospital with lower limb weakness, an inability to walk, vomiting, and a history of generalized body aches. The lower limb weakness and inability to walk began gradually 5 days prior. While at home, he reported collapsing five times and being unable to get up afterward, as his legs could not support his weight. These episodes were self-resolving, but they were becoming significantly prolonged. His past medical history was significant for recurrent episodes of lower limb paralysis that had occurred every month for the previous 2 years. These episodes often lasted for 2 minutes and were described as less severe, thus explaining why he never visited a hospital. Another aspect to note was a recent history of gastroenteritis, which may have exacerbated his GS symptoms at the time of presentation. The patient reported having vomited once and experienced diarrhea twice 1 day prior. Moreover, he had lost an estimated 10 kg in the previous few weeks as he was fasting for the month of Ramadan while maintaining a low carbohydrate, ketogenic diet with minimal intake of fluids. Similarly, he denied taking any medications, including diuretics. His family history was significant as his 19-year-old brother presented with similar symptoms at the age of 9 years and was subsequently diagnosed with GS.

Upon physical examination, he was fully conscious, alert, and oriented. His vital signs were stable with a slightly elevated heart rate of 103 beats per minute, a blood pressure of 113/74 mmHg, a temperature of 36.9 °C (oral), a respiratory rate of 18 breaths per minute, and an oxygen saturation of 98% on room air. He had a weight of 85 kg, a height of 170 cm, and a body mass index of 29.4 kg/m^2. On inspection, he had acanthosis nigricans on the posterior aspect of his neck, on his axillae, and both elbows. Auscultation of the heart revealed normal S1 and S2 heart sounds, with no added sounds, and the lungs revealed normal vesicular breathing bilaterally. Upon palpation of the abdomen, it was soft, lax, and nontender. A neurological examination of the lower limbs revealed a power of 2/5 with complaints of pain; however, the neurological examination of the upper limbs was unremarkable. There were no neurological focal deficits found.

Table 1 presents the venous blood gas (VBG) data taken from the patient in the ED. The results revealed a normal pH (7.43), normoglycemia (5.7 mmol/L), an elevated anion gap (13.9 mmol/L), a slight elevation in lactate (2.1 mmol/L), marked hypokalemia (1.7 mmol/L), normonatremia, and a reduction in both carbon dioxide (31.4 mmHg) and bicarbonate (28.8 mmol/L). As presented in Table 2, baseline laboratory investigations revealed a slightly elevated white blood cell count (WBC) (12.28×10^9/L; 75.3% neutrophils) and platelet count (464×10^9/L). Blood C-reactive protein (CRP) was 2.51 mg/L, which fell within the universally acceptable range. Liver function tests revealed an elevated alanine transaminase level (82 U/L). A remarkable fourfold increase in total creatine kinase was recorded (411 U/L). Importantly, laboratory analysis of serum electrolytes revealed hypomagnesemia (0.54 mmol/L), hypochloremia (93.4 mmol/L), hypokalemia (1.54 mmol/L), normonatremia H (139 mmol/L), and normocalcemia (2.32 mmol/L). Serum levels of renin and aldosterone were significantly elevated (128 ng/mL/hour and 62.7 pg/mL, respectively). Urine electrolyte analysis revealed hypermagnesuria (3.34 mmol/L), hypocalciuria (< 0.2 mmol/L), hypokaluria (13 mmol/L), high urinary chloride (161 mmol/L), and hypernatriuria (179 mmol/L),

Table 1 Venous blood gas at the time of presentation

	Patient's results	Normal range
pH	7.43	7.35–7.45
Glucose (mmol/L)	5.7	4–12
Anion gap (mmol/L)	13.9	4–12
BE (mmol/L)	7.7	+3 to −3
Lactate (mmol/L)	2.1	< 2
Potassium (mmol/L)	1.7	3.5–5
Sodium (mmol/L)	142	135–145
PCO_2 (mmHg)	31.4	41–51
HCO_3 (mmol/L)	28.9	20–24
PO_2 (mmHg)	31.4	30–40

BE base excess, PCO_2 partial pressure of carbon dioxide, PO_2 partial pressure of oxygen, HCO_3 bicarbonate

Table 2 Baseline laboratory investigations at the time of presentation

	Patient's results	Normal range
Hemoglobin (g/dL)	16.3	13.8–17.2
Hematocrit (%)	45.7	41–50
WBC (/L)	12.28×10^9	$4.5–11.0 \times 10^9$
Neutrophils (%)	75.3%	40–60
Platelet count (/L)	464×10^9	$150–450 \times 10^9$
CRP (mg/L)	2.51	< 0.3
HbA1C%	5.35	4–5.6
25-hydroxy vitamin D (nmol/L)	46.17	50–125
Alanine transaminase (U/L)	82	29–33
Total creatine kinase (U/L)	411	55–170
Creatinine (μmol/L)	72	61.9–114.9
Thyroid-stimulating hormone (mIU/L)	3.68	0.5–4.15
Thyroxine (pmol/L)	18.77	12–30
Serum magnesium (mmol/L)	0.54	0.85–1.1
Serum chloride (mmol/L)	93.4	95–105
Serum potassium (mmol/L)	1.54	3.5–5
Serum sodium (mmol/L)	139	135–145
Serum calcium (mmol/L)	2.32	2.2–2.7
HDL (mmol/L)	0.69	> 1
Triglyceride (mmol/L)	4.8	< 1.7
Cholesterol (mmol/L)	4.64	≤ 5
Renin (ng/mL/h)	128	4–23.7
Aldosterone (pg/mL)	62.7	3–28

WBC white blood cell, *CRP* C-reactive protein, *HDL* high-density lipoprotein

as presented in Table 3. A dexamethasone suppression test was done, which came back negative. An electrocardiogram (ECG) showed sinus rhythm and typical changes of hypokalemia with a prolonged QT interval, prominent U waves, and ST depression. Abdominal ultrasonography was performed, which revealed an enlarged fatty liver. No pathologies were seen in the gallbladder, spleen, pancreas, kidneys, or urinary bladder (Fig. 1).

In the ED, the patient was given 2.5 mg of intravenous magnesium sulfate, 500 mL of intravenous lactated Ringer's solution, 10 mg of intravenous metoclopramide, 40 mg of intravenous pantoprazole, and 1000 mg of

Table 3 Urine electrolyte levels at the time of presentation

	Patient's results	Normal range
Urinary magnesium (mmol/L)	3.34	0.86–9.54
Urinary calcium (mmol/L)	< 0.2	2.5–7.5
Urinary potassium (mmol/L)	13	≥ 20
Urinary chloride (mmol/L)	161	110–250
Urinary sodium (mmol/L)	179	> 20

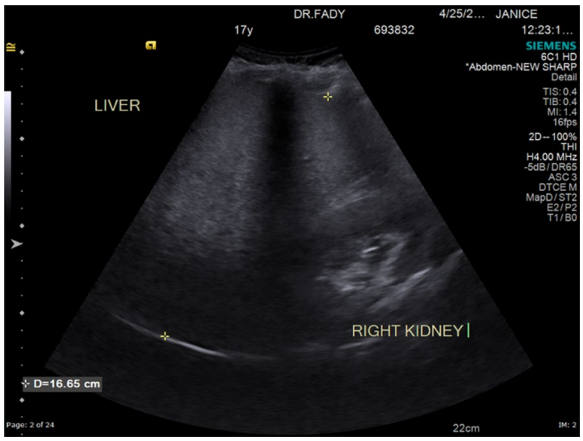

Fig. 1 Ultrasound image of the liver showing an enlarged fatty liver

intravenous acetaminophen. With these interventions, a gradual resolution of his lower limb weakness was noted. On the basis of the evaluation of the patient's symptoms, family history, physical examination, and laboratory investigations, the patient was diagnosed with GS. The patient was admitted to the HDU, where he received further electrolyte correction. He required 8 days of hospitalization, and prior to discharge, he received comprehensive patient education regarding his condition. The patient was discharged in good clinical condition and was administered daily potassium chloride (600 mg), calcium carbonate (600 mg), and spironolactone (25 mg) tablets. In addition, a follow-up appointment in the medical clinic was given to the patient 1 week after discharge.

Discussion

Gitelman syndrome is an autosomal recessive disorder typically caused by a mutation in the *SLC12A3* gene, which in most cases is classified as a missense mutation; therefore, this leads to a disruption in the thiazide-sensitive sodium chloride cotransporter (NCCT) [8]. According to numerous studies, the mutation of the *CLCNKB* gene can lead to a phenotypic overlap between GS and type III Bartter syndrome [9]. Clinical history, laboratory results, and genetic testing aid in differentiating between the two. The definitive diagnosis of GS, however, is through genetic testing [10]. In this case, the patient had a positive family history determined through genetic testing, which raised suspicions of a GS diagnosis.

Gitelman syndrome is a rare disorder that is estimated to have a prevalence of 25 per million people in the general population [11]. GS is known to affect individuals of different ethnic backgrounds. For instance, the prevalence of heterozygous individuals is approximately 1% of the white population [11]. However, there are no concise data regarding the exact prevalence of GS in other

ethnic groups. More importantly, there has been limited reported literature regarding any GS case within the MENA region, or any estimation of its prevalence.

Gitelman syndrome can manifest at any age from the neonatal period to adulthood, with a wide variety of presenting signs and symptoms. It either remains asymptomatic, has nonspecific symptoms, or it can present with the typical signs and symptoms of GS [12]. These symptoms include muscle cramps, muscle weakness, tetany, salt craving, mild polyuria, fatigue, dizziness, thirst, palpitations, or mild hypotension, among many others [13]. Clinical laboratory workups tend to aid in the diagnosis, illustrating salt and potassium wasting, metabolic alkalosis, hypokalemia, hypomagnesemia, and hypercalcemia [14]. These laboratory changes and symptoms were evident in this patient and aided in reaching a definitive diagnosis.

Gitelman syndrome is diagnosed by exclusion; thus, other differentials with similar presentations should be ruled out. These include laxative abuse; proton pump inhibitor (PPI) use; bulimia nervosa; primary hyperaldosteronism; Bartter syndrome (BS); and epilepsy, ataxia, sensorineural deafness, and salt wasting (EAST) syndrome.

Clinical history and urinalysis are extremely useful for excluding laxative abuse. Our patient denied the use of laxatives. He had a magnesium level of 3.3 mmol/L, potassium level of 13 mmol/L, and sodium level of 179 mmol/L, thereby excluding laxative abuse and confirming electrolyte wasting through urine and not through the gastrointestinal tract [15]. Likewise, PPI use can be easily excluded as it can cause isolated hypomagnesemia [16]. Eating disorders, such as bulimia nervosa, cause electrolyte imbalances but are associated with low urinary chloride. In this case, it was excluded, as urinary chloride was within normal limits (161 mmol/L) [17]. Primary hyperaldosteronism was also ruled out as it leads to low renin levels and hypertension, which were not evident in this patient [15].

Lastly, Bartter syndrome and Gitelman syndrome tend to have overlapping symptoms. The main differentiating factors that are present in BS are growth restriction and developmental delay [18]. Laboratory results tend to reveal hypercalciuria and normomagnesemia in patients with BS, while patients with GS present with hypocalciuria and hypercalcemia [18]. In this case, the patient's laboratory results revealed hypocalciuria and hypomagnesemia, thus leaning toward the diagnosis of GS [20]. Similarly, EAST syndrome was excluded because it is associated with neurologic symptoms, which were not observed in this patient [21]. After exclusion, GS was the most appropriate diagnosis for this patient after using clinical history, physical examination, laboratory results, and imaging to negate all the other causes. Individualized genetic testing for our patient would also have been a definite confirmatory test for GS, which was not done in this case [22]. However, it was previously performed for his elder brother and was positive for GS.

The treatment of GS is symptomatic, which is resolved through electrolyte supplementation. The mainstay treatment is incorporating a high sodium diet along with potassium and magnesium supplementation [7, 16]. Potassium chloride (KCL) is usually administered orally. However, if there is severe hypokalemia, as in this patient, we need to start urgent intravenous KCL infusion [23]. Similarly, oral magnesium chloride is frequently the supplement of choice owing to its better tolerability, and if severely deficient, it is promptly administered intravenously. Other treatment modalities include nonsteroidal anti-inflammatory drugs, potassium-sparing diuretics, and renin–angiotensin system blockers [16].

Conclusion

With the information presented in this report, it is vital for all health professionals to have a high index of suspicion of Gitelman syndrome as a differential diagnosis. This is owing to the nonspecific signs and symptoms of this disease that might be confused with other causes. A detailed patient history, clinical signs and symptoms, and laboratory workup are the cornerstones for a prompt diagnosis.

Abbreviations

GS	Gitelman syndrome
MENA	Middle East and North Africa
ED	Emergency department
HDU	High-dependency care unit
VBG	Venous blood gas
CRP	Blood C-reactive protein
ECG	Electrocardiogram
IV	Intravenous
PPI	Proton pump inhibitor
BS	Bartter syndrome
EAST	Epilepsy, ataxia, sensorineural deafness, and salt wasting
KCL	Potassium chloride
BE	Base excess
PCO_2	Partial pressure of carbon dioxide
PO_2	Partial pressure of oxygen
HCO_3	Bicarbonate
WBC	White blood cells
HDL	High-density lipoprotein

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Author contributions

HJT, NA, and KYA initiated the research, conducted the literature review, gathered the patient's data, and contributed to the writing of the initial manuscript. AEI took care of the patient, oversaw the research, and revised the initial

manuscript. AA supervised and contributed to the editing and revision of the initial manuscript. All the authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
Written informed consent was obtained from the patient for participation. This report was approved by the Ethics Committee of Sheikh Khalifa Medical City Ajman.

Consent for publication
Written informed consent was obtained from the patient for the publication of this report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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