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An Unusual Case of Weakness in an Adolescent

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Abstract

Gitelman Syndrome is one of the most frequently inherited renal tubular disorders. Due to a conglomerate of nonspecific symptoms, most patients are typically not diagnosed until adolescence [1]. We describe a case of Gitelman Syndrome misdiagnosed as a panic disorder and differentiate her underlying disease process from the iatrogenic effects of her initial treatment.

Presentation

A previously healthy 17-year-old female undergoes uncomplicated wisdom tooth extraction with intravenous midazolam sedation. The next day, she presents to an urgent care with shortness of breath and chest pain. The patient is diagnosed with panic disorder and prescribed low-dose benzodiazepine to manage her suspected anxiety symptoms. Incidental hypokalemia is also found, and the patient is prescribed oral potassium chloride supplements.

The patient presents to a local hospital 3 days later with fatigue, difficulty swallowing, poor oral intake, and continued shortness of breath. In addition, she now describes new onset of intermittent hand tremors and chest pressure.

Despite these complaints, the patient has a normal documented physical exam. Pupils are equal, round, and reactive to light. She is noted to have nonlabored breathing, normal heart sounds, and is coherent and oriented to questioning. Her initial laboratory results are significant for hypokalemia with potassium of 2.8 mmol/L (reference range: 3.5-5.5 mmol/L) and hypomagnesemia with magnesium of 1.4 mg/dL (reference range: 1.5-2.3 mg/dL). A computerized tomography (CT) angiogram is normal without radiographic findings for pulmonary embolism, CT neck is normal without abscesses or other foci of infection, and CT head is normal without space-occupying lesions (Table 1).

Table 1: Laboratory Results (Initial).

Sodium	138	136-145 mmol/L
Potassium	2.8 (L)	3.5-5.5 mmol/L
Chloride	105	95-105 mmol/L
Bicarbonate	25	25-35 mmol/L
Calcium	8.8 (L)	8.9-10.7 mg/dL
Magnesium	1.4 (L)	1.5-2.3 mg/dL
Phosphorus	3.4	2.3-4.8 mg/dL

She is admitted to the hospital for intravenous fluids and electrolyte monitoring. She receives scheduled clonazepam for anxiety and requires frequent oral and intravenous replacement of potassium, calcium, and magnesium. She also receives dexamethasone to treat potential postoperative oral cavity swelling that may be contributing to her dysphagia despite a normal oropharyngeal exam. After one week of hospitalization, she develops altered mental status, bradycardia, and horizontal nystagmus. Electrocardiogram (EKG) shows sinus bradycardia to 38 beats per minute. She is transferred to a tertiary Children's hospital for evaluation and treatment (Figure 1).

On arrival to our facility, the patient appears ill and lethargic. Soft tissue swelling and pain of bilateral mandibular areas are noted on her head and neck exam. Both eyes exhibit horizontal

nystagmus. Patient also endorses photophobia which limits her pupil exam. Facial muscles, upper and lower extremity movements are symmetric. Heart rate is bradycardic at 58 beats/minute with normal heart sounds. The patient endorses generalized muscle tenderness to palpation. Electrolytes are repeated with significant findings of continued hypokalemia, hypocalcemia, and hypomagnesemia (Table 2).

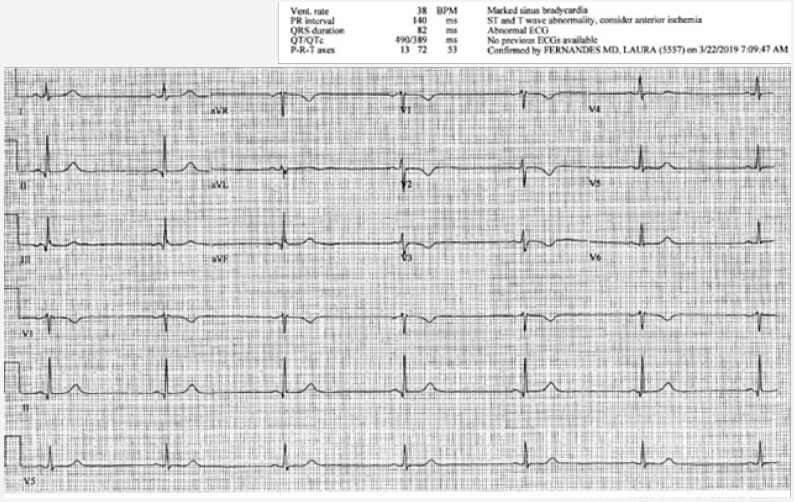

Figure 1: Electrocardiogram Result.

Table 2: Laboratory Results (Repeated).

Sodium	139	136-145 mmol/L
Potassium	2.5 (L)	3.5-5.5 mmol/L
Chloride	105	95-105 mmol/L
Bicarbonate	25	25-35 mmol/L
Calcium	8.2 (L)	8.9-10.7 mg/dL
Magnesium	1.4 (L)	1.5-2.3 mg/dL
Phosphorus	4	2.3-4.8 mg/dL

Upon further chart review, the patient has a documented low magnesium at age 7 and a documented low potassium at age 10.

Discussion

Differential Diagnosis

The differential diagnosis for altered mental status and bradycardia at this point is broad. The most critical etiologies worth considering include intracranial pathologies such as meningitis, thrombosis, or hypoxic/ischemic neurologic insult during the wisdom tooth extraction. This consideration is unlikely given her waxing and waning clinical course, nonfocal neurological exam, and prior normal cranial imaging. Another important consideration is cardiogenic shock causing bradycardia with poor perfusion to the brain. This is also incongruent with her overall hospital course as the bradycardia followed her initial complaints. At this juncture, the patient has her initial complaints of fatigue, dysphagia, chest pressure, and hand tremors, with an entirely new set of physical findings: altered mental status, sinus bradycardia, and horizontal nystagmus. Since these new symptoms evolved over the course of a week while receiving scheduled benzodiazepines, it is possible that these new symptoms are secondary drug effects and not caused by evolution of her underlying disease process.

The most striking feature of her inpatient stay at another hospital is the repeated electrolyte replacement of potassium, calcium, and magnesium. An electrolyte disturbance could cause her initial nonspecific symptoms and raises the question of an endocrine disorder such as hypothyroidism or hypoparathyroidism or a rheumatologic disorder such as systemic lupus erythematosus. At this point, our suspicion is that she most likely has a previously undiagnosed renal tubulopathy (e.g., Bartter or Gitelman syndrome) given her electrolyte imbalance refractory to repletion that was exacerbated by her decreased oral intake.

Patient course

She has further evaluation of her altered mental status with a repeat CT head, magnetic resonance imaging (MRI) of the brain, and lumbar puncture with cerebral spinal fluid studies which are all normal. Her cardiac evaluation including echocardiogram and EKG are unrevealing. Parathyroid hormone and thyroid studies are also normal. Her renal ultrasound is normal. Her neurological symptoms resolve with the discontinuation of benzodiazepines and continued electrolyte replacement. Urine studies show renal magnesium wasting, and genetic testing reveals a biallelic mutation in SLC12A3 that indicates Gitelman syndrome. Her hypocalcemia is initially attributed to persistent hypomagnesemia, but her PTH is normal and lab studies reveal vitamin D 25-hydroxylase deficiency. Her normal bicarbonate level on hospital admission is attributed to outpatient potassium chloride supplementation, explaining her lack of metabolic alkalosis on presentation. She is discharged on magnesium, potassium, calcium, and vitamin D supplements.

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The Condition

Gitelman Syndrome (GS), also known as familial hypokalemia-hypomagnesemia, is an inherited recessive tubulopathy [2]. It is one of the most frequently inherited renal tubular disorders. The most common mutation involves the loss of function in the SLC12A3 gene which encodes the thiazide-sensitive sodium chloride cotransporter (NCC) [3,4].

Due to the affected NCC, patients with GS have a propensity for electrolyte wasting and exhibit hypokalemia, hypomagnesemia, metabolic alkalosis, hypocalciuria, and hyperreninemic hyperaldosteronism [3,5,6]. In medical situations involving a significant loss of gastric or intestinal secretions [5], patients can present with clinical symptoms such as low blood pressure and hypotension due to extracellular volume depletion, mild polyuria or nocturia due to derrangements in urinary concentration, cardiac arrhythmia and prolonged QT in the context of hypomagnesemia and alkalosis [7,8], and/or nonspecific symptoms such as muscle cramps, dizziness, fatigue, paresthesias, palpitations, polyuria, and muscle tetany [9]. In affected individuals, the initiation of diuretics/laxatives or withholding oral intake can often provoke onset of symptoms. Hypokalemia and hypomagnesemia should be corrected in order to prevent the development of rare but life-threatening ventricular arrhythmias [7,10,11].

Treatment/Management

Despite its chronicity, the prognosis for patients with GS is typically very good provided patients receive routine ambulatory monitoring. GS rarely leads to development of chronic nephropathy, unlike its more severe variant: Bartter's Syndrome [12]. Patients require potassium and magnesium supplementation to achieve at least low normal lab levels in the blood. Occasionally, potassium sparing diuretics are employed in ameliorating hypokalemia and hypomagnesemia [3,13]. Lifestyle adjustments aimed at increasing dietary intake of magnesium, potassium, and sodium are recommended to address underlying subclinical electrolyte abnormalities [14]. Although clinical symptoms are typically benign, there exists evidence that most patients report a poor quality of life due to wide variations in neuromuscular symptoms that impact their daily activities [9]. These patients warrant lifelong close follow-up to monitor and manage medico-psychological implications.

Summary

This case presents a previously healthy female with findings of hypokalemia, hypomagnesemia, fatigue, muscle cramps, and dizziness in context of decreased oral intake following wisdom tooth extraction. After discriminating drug effect from initial symptoms, she is diagnosed with GS caused by a mutation in SLC12A3 responsible for the thiazide-sensitive sodium chloride cotransporter. She is also diagnosed with vitamin D 25-hydroxylase deficiency which highlights the importance of complete laboratory evaluation of electrolyte disturbances to determine the most appropriate treatment.

Due to the challenges inherent to a complex diagnosis that presents with a conglomerate of nonspecific symptoms, most patients with this condition are typically diagnosed later in adolescence[1]. Patients with GS can become acutely ill with significant volume loss and present with life-threatening electrolyte derangements due to their inherited tendency toward electrolyte wasting. It is worthwhile for clinicians to consider Gitelman Syndrome when patients present with disproportionate, unexplained, and refractory hypokalemia, hypomagnesemia, and metabolic alkalosis.

Author Disclosure

Drs He, Davis, and Elenberg have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Author Contributions

SH conceived the case report, drafted the manuscript, performed the literature review, and approved the final manuscript.

KD conceived the case report, drafted the manuscript, and approved the final manuscript.

EE helped to draft the manuscript and approved the final manuscript.

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