An Adolescent with Tingling and Numbness of Hand: Gitelman Syndrome

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Abstract

Context: Gitelman syndrome is an inherited autosomal recessive disorder. It is usually diagnosed incidentally during adolescence or early adulthood based on clinical and biochemical findings. Case Report: We present a case of a 16-year-old adolescent female presenting with recurrent chest pain, tingling, and numbness of bilateral hands. Diagnosis was established by the typical biochemical abnormalities with hypokalemia, hypomagnesemia, hypocalciuria, metabolic alkalosis, and hyperreninemic hyperaldosteronism. Genetic diagnosis was confirmed by sequence analysis of the SLC12A3 gene showing the compound heterozygous mutation encoding the thiazide-sensitive sodium chloride co-transporter. Conclusion: Gitelman syndrome should be considered as a differential diagnosis in the workup of hypokalemia, especially in adolescent age group. The presence of hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria, and mutation analysis provides the final diagnosis.

Keywords: Adolescent, Gitelman syndrome, Hyperreninemic hyperaldosteronism, Hypokalemia

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Introduction

Gitelman syndrome (GS) is an inherited renal tubular disorder characterized by hypokalemia, alkalosis, and hypertrophy of the juxtaglomerular complex with secondary hyperaldosteronism.[1] The mode of inheritance is autosomal recessive. Gitelman syndrome results from dysfunctional Na-Cl transporters in the distal convoluted tubule, which results in failure to conserve potassium and magnesium.[2] Secondary biological adaptations of downstream tubular segments in collecting ducts are responsible for alkalosis, renin-aldosterone activation, and prostaglandin hypersecretion. The first clinical presentation is usually observed during childhood or adolescence and may include transient episodes of weakness, paresthesia. The course of disease is generally mild, and some patients even remain asymptomatic.

Case Presentation

A 16-year-old Asian American female presented to emergency room with numbness over all four extremities for 1 week. She had no history of medication usage, including diuretics and laxative. There was no history of developmental delays. Patient was attending ninth grade with average school performance. There was no family history of GS, developmental delays or malnutrition issues. Her height was at tenth percentile, weight at fifteenth percentile, and BMI at tenth percentile. Neurologic examination revealed no sensory or motor deficit. Other system examinations were found to be normal. Laboratory results showed hypokalemia (2.3 mmol/L), metabolic alkalosis (pH 7.48, and bicarbonate 33 mmol/L), and hypomagnesemia (1.2 mmol/L). Further evaluation was initiated by pediatric nephrology service to find out cause of hypokalemia. Her supine plasma renin to be 25 ng/ml/hour (normal range, 2.47-2.23 ng/ml/hour), supine aldosterone 7.2 pg/ml (normal range, 1-16 pg/ml). The daily excretions of potassium and calcium were
99 mmol/day and 32.8 mg/day, respectively. The urine calcium/creatinine ratio was 0.04. She was treated with oral magnesium (900 mg/day), potassium (60 mmol/day) and amiloride 5 mg daily. Tingling and numbness of extremities resolved and potassium/magnesium serum levels normalized (potassium 3.7 mmol/L and magnesium 1.8 mmol/L) within 7 days of treatment. Patient was discharged home on same daily doses of amiloride, potassium and magnesium supplementation. Genetic diagnosis was confirmed by sequence analysis of the SLC12A3 gene showing the compound heterozygous mutation encoding the thiazide-sensitive sodium chloride co-transporter.

Discussion

The electrolyte abnormalities induced by thiazide diuretics and GS were found to be similar. The Na-Cl co-transporters (NCCT) are found to be dysfunctional in GS. Epidemiologic studies have demonstrated that there is no ethnic predilection for GS, and both sexes are equally affected. Simon et al. first demonstrated complete linkage of GS to the NCCT gene; human gene maps SLC12A3 on chromosome 16q13 and specified GS as an autosomal recessive disorder with 99% penetrance. The defect in NCCT leads to sodium chloride (NaCl) wasting and hypovolemia, which stimulates the renin-angiotensin-aldosterone system, and causes an increase in apical Na reabsorption and stimulation of the basolateral Na-K-ATPase. The elevated aldosterone levels also stimulate H-ATPase pumps in the cortical and medullary collecting ducts, leading to increased apical H secretion. K and H excretion increases as K-enters from the basolateral membrane via the Na-K-ATPase pumps, resulting in hypokalemic metabolic alkalosis. Sodium reabsorption via sodium channels is accompanied by potassium and hydrogen ion excretion, resulting in further hypokalemia and metabolic alkalosis. NaCl uptake through the apical membrane decreases, whereas intracellular Na continuously leaves the cells through the Na-K-ATPase at the basolateral membrane. This extrusion of Na reduces intracellular Na concentration, thereby hyperpolarizing distal convoluted tubular cells and causing Ca2+ to enter the apical membrane through Ca2+ channels. Similarly, loss of NCCT function can inhibit reabsorption of magnesium via an apical Na/Mg exchanger. Because distal convoluted tubules reabsorb approximately 5% of filtered magnesium and the reabsorption is load-dependent, impairment in magnesium reabsorption in this segment would be expected to result in magnesium wasting and hypomagnesaemia.

Patients with GS do not have symptoms throughout infancy and the preschool years. They are often diagnosed in adolescence or early adulthood. This disorder may be diagnosed as an incidental finding during laboratory investigation in asymptomatic patients or patients with intermittent mild symptoms of muscle weakness, fatigue, cramps. Severe symptoms such as tetany, rhabdomyolysis, and paralysis have been reported. In our case, patient was brought to the emergency room at the middle of night with acute severe tingling and numbness of hands. When elaborate past medical history was obtained after hospital admission; she reported mild intermittent tingling and numbness of hands for many years but never been reported to the primary care doctor. There were no additional factors in her case to explain acuteness of presentation. The most common reported symptoms were salt craving (95%), musculoskeletal symptoms such as cramps (84%), muscle weakness and aches (70%), and constitutional symptoms such as fatigue (82%), dizziness (80%), nocturia (80%), and polydipsia (65%). Almost all GS patients have hypokalemia, hypomagnesemia, metabolic alkalosis, and markedly reduced urinary calcium excretion. The ratio of urinary calcium to urine creatinine less than 0.1.

GS is differentiated from Bartter syndrome by severity of clinical presentation and laboratory findings. Patients with Bartter syndrome typically present before the age of 6 years with severe symptoms such as dehydration and growth retardation. Serum magnesium and urinary calcium findings distinguish GS from Bartter syndrome, with GS denoting the subset with hypomagnesemia and hypocalciuria. In addition, genetic analysis may further differentiate the two syndromes with complete linkage of GS to the locus encoding NCCT on chromosome 16q13. The mainstay treatment for GS is oral potassium and magnesium supplementation. The addition of potassium-sparing diuretics helps retrieving potassium loss from distal and collecting segment of renal tubules. Magnesium therapy not only corrects the hypomagnesaemia but also improves hypokalemia.

Long-term prognosis for renal function and life expectancy is excellent in GS patients.

In conclusion, GS should be considered as a differential diagnosis in work up of hypokalemia, especially in adolescent age group. The presence of hypokalemia, metabolic alkalosis, hypomagnesaemia, hypocalciuria, and mutation analysis provides the final diagnosis.

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