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Gitelman syndrome

David Steflík MD

Overview

Gitelman syndrome, also known as familial hypokalemia-hypomagnesemia, is an autosomal recessive renal tubular salt-wasting disorder characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria.

Epidemiology

Gitelman is the most common renal tubular disorder among Caucasians, with a prevalence of 1 in 40000. It is transmitted as an autosomal recessive trait, with the prevalence of heterozygotes at approximately 1% in the Caucasian population.¹

Pathophysiology

In the majority of cases, Gitelman syndrome is caused by mutations in the SLC12A3 gene, which encodes the renal thiazide-sensitive sodium-chloride co-transporter that is present in the distal convoluted tubule.² In comparison, the related Bartter syndrome is primarily a defect of transporters in the thick ascending Loop of Henle, mainly the Na-K-2Cl cotransporter.

It may be useful to consider Gitelman a defect of the transporter where thiazide diuretics work, and Bartter a defect where loop diuretics work. In a quick physiology refresher, thiazide diuretics inhibit the sodium-chloride co-transporter in the early distal tubule. Loop diuretics inhibit the sodium-2 chloride-potassium co-transporter in the thick ascending loop of Henle.

Clinical Presentation

In contrast to Bartter syndrome, which is usually diagnosed in infancy or early childhood (before the age of 5) because of failure to thrive, Gitelman usually does not affect growth and typically presents in late childhood to adulthood. It commonly presents with cramps of the arms and legs, fatigue, ranging from mild to severe, seizures, polyuria and nocturia, chondrocalcinosis, growth retardation if presents younger, and hypertension later in life.³ Prolonged Qtc and arrhythmias with resultant palpitations and/or syncope has been estimated to occur in half of affected patients.⁴

Differential diagnosis

There are a limited number of conditions that present with metabolic alkalosis and hypokalemia. Prolonged vomiting (hyperemesis) and diuretic use can both present with metabolic alkalosis and hypokalemia. Hyperemesis can be differentiated from Gitelman syndrome by characteristic physical exam findings along with a urine chloride concentration <25 meq/L in vomiting. Urine chloride concentration is high in Gitelman syndrome, often >40 meq/L. Sjogren syndrome can also cause electrolyte abnormalities resembling Gitelman syndrome. Another cause is administration of nephrotoxic agents such as cisplatin. Less common causes of metabolic alkalosis and hypokalemia include undiagnosed cystic fibrosis and infants given chloride deficient liquid formula.³

Diagnostic evaluation

Due to the relative rarity of Gitelman syndrome, it rarely is considered in the initial differential of weakness, paresthesias, or seizures. However, it must be considered if serum electrolytes

show a metabolic alkalosis and hypokalemia, with corresponding low magnesium. Further workup should then include a spot urine calcium to creatinine ratio (Ca/Cr). A low ratio for age, or normal calcium concentrations in the urine is expected in Gitelman syndrome. A high ratio of calcium to creatinine, or a high 24 hour urine collection, supports the diagnosis of Bartter syndrome. The expected calcium excretion greatly varies with age, so appropriate lab cut-offs should be used to assess for hypercalciuria.⁵

EKG to assess for prolonged Qtc and risk of ventricular arrhythmias should be performed. In a study of 21 patients with Gitelman syndrome, 11 had prolonged Qtc and therefore were at high risk for ventricular arrhythmias.⁴

Genetic testing is not routinely performed, but mutations in the SLC12A3 gene correlate with mutations in the thiazide sensitive Na-Cl cotransporter.⁶ The National Center for Biotechnology Information will have up to date information regarding labs offering this genetic testing.

Treatment

Treatment of Gitelman consists of correcting the electrolyte disturbances which improves the quality of life in these patients by decreasing fatigue, cramping, and risk of cardiac arrhythmias. The first mainstay of therapy is magnesium and potassium supplementation, with magnesium supplementation being necessary to augment potassium normalization. However, serum magnesium normalization is difficult to obtain because high doses of magnesium cause diarrhea.⁷ One group recommends magnesium chloride orally at doses of 3mmol Mg/m²/24hrs or 4-5 mg/kg/24hours.² The dose should be divided into 3-4 doses throughout the day to help prevent diarrhea and adjusted according to serum magnesium levels. Similar to patients receiving steroids for adrenal insufficiency, the magnesium supplementation may have to be increased during periods of illness, especially those with a component of vomiting and diarrhea.

The second mainstay of therapy is with a potassium sparing, direct aldosterone antagonist such as Spironolactone. Spironolactone has been shown to be more effective than amiloride in correcting the hypokalemia.⁸ Unlike Bartter, the defect in Gitelman syndrome does not increase renal prostaglandin E2 production so NSAIDS are of no benefit in treatment.⁹

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