Case Report

Gitelman Syndrome as a Cause of Psychomotor Retardation in a Toddler

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Abstract

Introduction: Gitelman syndrome (GS) is a very rare autosomal recessive tubulopathy due to loss-of-function or mutation in solute carrier family 12, member 3 gene (SLC12A3 gene) encoding thiazide-sensitive NaCl co-transporter in the distal convoluted tubule, leading to hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria and low-to-normal blood pressure. Clinical signs are mostly secondary to chronic hypokalemia and include dizziness, fatigue, constipation and weakness. Patients can also present with muscle cramps, tetany, fatigue and convulsions due to severe metabolic alkalosis or hypomagnesemia. Manifestations of GS are rarely apparent before the age of five, and the syndrome is usually diagnosed during adolescence or adulthood. Here we describe a case of GS presenting in infancy with hypokalemia and psychomotor retardation.

Case Report: We present an 18-month-old boy who presented with psychomotor retardation and failure to thrive. Investigations revealed hypokalemia at 2.7 mmol/L, metabolic alkalosis, hypocalciuria and normal serum magnesium level. The diagnoses of Barter syndrome (BS) and Gitelman syndrome (GS) were considered. Genetic studies confirmed the diagnosis of GS and three different mutations of in SLC12A3 gene were detected. Two mutations (c.2576T>C and c.2929C>Ty) were considered as causal ones, with the patient’s parents being the heterozygous carriers. Oral potassium supplementation resulted in normalisation of the hypokalemia and psychomotor improvement.

Conclusion: We report a rare case of psychomotor retardation occurring at an early age in genetically confirmed GS. In spite of being a rare disorder, GS has to be considered in children with developmental delay and muscle weakness. With adequate treatment, GS patients have an excellent prognosis.

Keywords: Gitelman Syndrome; Potassium; Hypokalemia; Psychomotor Retardation

The authors declared no conflict of interest

Introduction

Gitelman syndrome (GS) is an autosomal recessive tubulopathy due to loss-of-function / mutation in solute carrier family 12, member 3 gene (SLC12A3 gene) encoding thiazide-sensitive NaCl co-transporter in the distal convoluted tubule [13]. GS is a rare condition with a prevalence of 1:40 000. The prevalence of heterozygotes is approximately 1% in Caucasian populations. GS is characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria and low-to-normal blood pressure [1-3]. Bartter syndrome (BS), especially type III, is the most important genetic disorder to consider in the differential diagnosis of GS. The biochemical features of both syndromes include hypokalemic hypochloremic metabolic alkalosis associated with high plasma renin activity and high aldosterone concentration [3]. Both patients with BS and GS present with complaints of constipation, muscle cramps and weakness secondary to chronic hypokalemia. Patients with either syndrome may also present with non-specific dizziness and fatigue [3]. GS is usually diagnosed during adolescence or adulthood and clinical signs are rarely apparent before the age of five. It is also associated with less severe failure to thrive and milder growth retardation [1-3]. In contrast, patients with BS present in early childhood and they often have severe failure to thrive and growth retardation [3].

Case Report

We present an 18-month-old boy who was referred to the pediatric tertiary healthcare center because of psychomotor retardation. Investigations revealed hypokalemia at 2.7 mmol/L, metabolic alkalosis, hypocalciuria and normal serum magnesium level. The diagnoses of Barter syndrome (BS) and Gitelman syndrome (GS) were considered. Genetic studies confirmed the diagnosis of GS and three different mutations of in SLC12A3 gene were detected. Two mutations (c.2576T>C and c.2929C>Ty) were considered as causal ones, with the patient’s parents being the heterozygous carriers. Oral potassium supplementation resulted in normalisation of the hypokalemia and psychomotor improvement.

Conclusion: We report a rare case of psychomotor retardation occurring at an early age in genetically confirmed GS. In spite of being a rare disorder, GS has to be considered in children with developmental delay and muscle weakness. With adequate treatment, GS patients have an excellent prognosis.

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his birth length was 48 cm and postnatal adaptation was uneventful. Psychomotor retardation was noticed at the age of four months. By the age of 12 months he was still unable to sit, stand up or crawl. Parents sought medical advice and at the age of 14 months he was referred for rehabilitation. There was still no improvement after four months of rehabilitation and at the age of 18 months he was referred for further pediatric evaluation. When seen at our center, his height was 84.5 cm (0 standard deviation (SD)), body weight was 9.05 kg (-2.2 SD) and body mass index was 12.7 (-2.5 SD). Basic laboratory evaluation revealed hypokalemia with a serum potassium level of 2.7 mmol/L, metabolic alkalosis with a pH of 7.48 and base excess of + 2.2 mmol/L and hypocalciuria with a urinary calcium/creatinine ratio below 0.1 mmol/mmol (normal range 0.1-1.0 mmol/mmol). The serum levels of sodium, calcium and magnesium were within normal reference range. The serum level of aldosterone was high at 1.9 nmol/L (normal level < 0.94 nmol/L). Serum levels of free thyroxine and thyroid-stimulating hormone were normal. Screening tests for inborn errors of metabolism and magnetic resonance imaging of the brain were all normal. A diagnosis of GS was considered and later confirmed by genetic analysis. Three different mutations of SLC12A3 gene were detected. Two mutations (c.2576T>C and c.2929C>T) were considered as causal mutations with the patient’s parents being the heterozygous carriers. Oral supplementation with potassium chloride was started, resulting in normalisation of serum potassium level (3.5 mmol/L). Within one month of supplementation a significant psychomotor improvement was apparent and the rehabilitation care could be discontinued at the age of 20 months. Currently, the boy is 6 years old with normal level of psychomotor development. Body height and weight are at the third percentile of the reference population. He is taking potassium chloride and spironolactone on a daily basis. Lifelong supplementation of magnesium is often needed. Potassium sparring diuretics such as amiloride and spironolactone may be effective in ameliorating hypokalemia and hypomagnesemia [2-3]. Cardiac work-up is appropriate to screen for risk factors of cardiac arrhythmias [2].

The long-term prognosis of GS is usually good. In general, growth is normal but can be delayed in those GS patients with severe hypokalemia and hypomagnesemia [2, 3, 5-7]. This particular patient presented with developmental delay at the age of four months and hypokalemia was diagnosed at the age of 18 months. In children, there have been only scarce reports on GS with clinically manifest hypokalemia. In a report by Tamaro et al hypokalemia was detected in the first month of life in two pairs of prematurely born twins with GS [8]. Sinha et al reported a case of GS with a novel homozygous mutation in the SLC12A3 gene, presenting with fatigue, paresthesias, weakness of limbs and neck muscles at the age of 2.5 years [9]. Conti presented a 9-year-old girl with GS who had fatigue, numbness and weakness of both legs, she was erroneously diagnosed as a Bartter syndrome at one year of age [10]. A report by Galli-Tsimopoulou presented a 10-year old girl with GS who presented with persistent unexplained hypokalemia and no severe clinical symptoms [11]. Similarly, Chan et al reported an asymptomatic 8-year-old GS girl where hypokalemia was detected accidentally prior to appendectomy [12].

Discussion
GS is transmitted as an autosomal recessive trait. Mutations in the solute carrier family 12, member 3 gene, SLC12A3, which encodes the thiazide-sensitive NaCl co-transporter (NCC), are found in the majority of GS patients. Currently, more than 140 different NCC mutations throughout the whole protein have been identified. In few GS patients, mutations in the CLCNKB gene, encoding the chloride channel CIC-Kb have been detected. Disruption of the distal tubular channel activity leads to electrolyte wasting. The effective low extracellular volume can also activate the renin-angiotensin-aldosterone system [1-3].

Clinical manifestations consist of transient periods of muscle weakness and tetany, accompanied by abdominal pain, vomiting and fever. Paresthesias, especially in the face, frequently occur. Surprisingly, some patients are completely asymptomatic except for chondrocalcinosis due to deposition of calcium pyrophosphate dehydrate crystals in synovium and synovial fluid that causes swelling, local heat, and tenderness over the affected joints. Blood pressure is lower than that in the general population [2-3]. Severe neuromuscular manifestations, growth retardation and sudden cardiac arrest due to ventricular arrhythmias have also been reported in GS patients, suggesting that GS is not an asymptomatic disease and can adversely affect quality of life [4-6]. In most of GS patients, symptoms rarely appear before the age of six years and the disease is diagnosed during adolescence or adulthood. Diagnosis is based on the clinical symptoms and biochemical abnormalities (hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria). Bartter syndrome (especially type III) is the most important genetic disorder to consider in the differential diagnosis of GS. GS patients are encouraged to maintain a high-sodium and high potassium diet [2-5]. Lifelong supplementation of magnesium is often needed. Potassium sparring diuretics such as amiloride and spironolactone may be effective in ameliorating hypokalemia and hypomagnesemia [2-3]. Cardiac work-up is appropriate to screen for risk factors of cardiac arrhythmias [2].

In a report by Skalova, Neuman, Lnenicka and Stekrova, et al hypocholesterolemia was detected accidentally prior to appendectomy [12].
yet another paper, Tuhta and his colleagues described an 18-year-old girl with GS and history of muscle weakness and transient tetanic episodes affecting both hands lasting for two years [13]. Furthermore, hypokalemia-associated rhabdomyolysis can also develop in children with GS, as observed in a 13-year-old girl who presented with weakness of the extremities, walking difficulty and calf pain [14].

**Conclusion**

We report a rare case of psychomotor retardation occurring at an early age in genetically confirmed GS. In spite of being a rare disorder, GS has to be considered in children with developmental delay and muscle weakness. With adequate treatment, GS patients have an excellent prognosis.

**References**


