CASE REPORT

Gitelman syndrome: First report of genetically established diagnosis in Greece

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Abstract

Gitelman syndrome is an inherited renal tubular disorder characterized by hypokalemic metabolic alkalosis. It is distinguished from other hypokalemic tubulopathies, such as Bartter syndrome, by the presence of both hypomagnesemia and hypocalciuria. We report a case of Gitelman syndrome in a 10-year-old girl who presented for examination of persistent unexplained hypokalemia. She had no severe clinical symptoms but she had typical laboratory findings including hypokalemia, hypomagnesemia and normocalcemic hypocalciuria. Molecular analysis revealed a mutation in the exon 21 of the SLC12A3 gene which encodes the thiazide-sensitive sodium-chloride co-transporter expressed in the distal convoluted tubule (a guanine to adenosine substitution at nucleotide 2538). She was treated with oral potassium and magnesium supplements. This is the first report of genetically established diagnosis in Greece. Gitelman syndrome should be considered as a cause of persistent hypokalemia and genetic analysis might be a useful tool to confirm the diagnosis. Hippokratia 2010; 14 (1): 42-44

Key words: Gitelman syndrome, hypokalemia, hypocalciuria, hypomagnesemia

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Gitelman syndrome (GS, OMIM: 263800) is a rare autosomal recessive inherited renal tubular disorder. It is caused by inactivating mutations in the SLC12A3 gene that encodes the thiazide-sensitive sodium-chloride co-transporter (NCCT or TSC) expressed in the distal convoluted tubule of the kidney[1]. It is characterized by hypokalemic alkalosis, also found in Bartter syndrome (BS), but the hypomagnesemia and normocalcemic hypocalciuria are the typical biochemical findings that distinguish it from the "classical" BS[1,2]. Main symptoms include mild muscular weakness and cramps, occasional episodes of tetany, constipation, abdominal pain and vomiting[3,4]. Patients are often diagnosed in adulthood during routine laboratory investigation due to lack of severe clinical features. We report the first genetically confirmed case of GS in Greece.

Case report

A 10-year-old Greek girl was referred to our department in April, 2005 due to persistent hypokalemia of unknown origin. Her hypokalemia had first been incidentally detected one year ago when she was admitted to a primary care health unit for evaluation of severe constipation. Until then, she had been free from symptoms. She was readmitted to the same hospital 2 weeks ago because she started complaining of diarrheas, abdominal pain and high temperature. A febrile gastroenteritis accompanied with persistent hypokalemia was diagnosed at that time.

There was nothing remarkable recorded neither from the patient's medical history nor from her family history. She denied any medication usage including laxatives or diuretics. She was delivered uneventfully at term, with normal prenatal history. Her birth weight as well as birth length were within normal percentiles. The marriage of her parents was not consanguineous.

At the time of admission in our tertiary department, physical examination revealed a well-developed female with no signs of dehydration or skin hyperpigmentation. Her height was 137 cm (25th to 50th percentile) and weight 34 kg (50th percentile). Her blood pressure was 100/70 mmHg and pulse rate 90 beats/min. Cardiovascular examination showed a regular rate and rhythm without murmurs or gallops. She had neither hepatosplenomegaly nor peripheral edema. Neurologic examination showed no sensory or motor disorder.

Laboratory tests revealed normal leukocyte, erythrocyte and platelet count. Blood urea nitrogen (BUN) was 38 mg/dl, creatinine (Cr) 0.53 mg/dl and glucose 85mg/dl. Serum electrolyte concentrations were as follows: sodium (Na^+) 139 mEq/L, potassium ($K^{+)}$ 2.7 mEq/L, chloride (Cl^-) 92 mEq/L, calcium (Ca^{+2}) 9.86 mg/dl, phosphorus (P) 3.6 mg/dl, magnesium (Mg^{+2}) 1.2 mg/dl. Analysis of 24 h urine collection revealed: extremely decreased calcium excretion (6 mg/d or 0.17 mg/kg/d), increased potassium excretion (310 mEq/d) and normal sodium, chloride, and phosphorus values.

The calculated urine calcium/creatinine ratio was lower than 0.1. Analysis of the arterial blood gasses showed metabolic alkalosis (PH: 7.49, bicarbonate: $HCO3^-$ 29.4 mEq/L). The aldosterone serum level was high (100 ng/dl, normal range for age: 4-44 ng/dl) as well as the plasma renin activity (10.1ng/ml/h, normal range for age: 0.5-5.9 ng/ml/h). Serum parathyroid hormone level was within normal range (20 ng/dl). No pathological signs were found in the electrocardiogram, chest X-ray and renal ultrasound.

Using the diagnostic criteria of Bettinelli et al (urinary calcium to creatinine ratio < 0.1 and plasma magnesium < 0.65 mmol/L)[5] a clinical diagnosis of GS was suspected. Therefore, DNA analysis for detection of NCCT gene mutations was performed sending the patient's blood sample in the laboratory of the Nephrology Department of the Tri-Service Hospital of Taipei, Taiwan. Using genomic DNA from peripheral blood cells, the 26 exons of the gene were amplified by the polymerase chain reaction and the products were completely sequenced by direct sequencing. A mutation was detected in the exon 21 of NCCT gene. A guanine to adenosine substitution was identified at nucleotide 2538 (G2538A, TGG to TGA). This mutation results in a premature stop codon from tryptophan at codon 844 (W844stop) in the intracellular carboxyl terminus of the gene product. Accordingly, the diagnosis of Gitelman syndrome was confirmed.

Treatment with oral supplementation of potassium and magnesium was initiated during hospitalisation of the patient. The plasma potassium and magnesium levels were improved gradually and finally normalized. At present, the patient is maintained on oral magnesium and potassium preparations but both serum electrolytes levels remain borderline low.

Discussion

In 1962 Bartter et al[6] described a syndrome characterized by hypertrophy and hyperplasia of the juxtaglomerular apparatus of the kidneys and overproduction of renin, angiotensin and aldosterone. The two male patients (5 and 25 years old respectively) reported then had a history of slow growth, polydipsia, polyuria, enuresis and weakness. Both of them had normal blood pressure. The syndrome was associated with hypokalemic alkalosis.

In 1966 Gitelman et al[7] described three adult female patients with occasional episodes of muscle weakness and tetany. Neither growth retardation nor polyuria were detected. Hypokalemia, hypomagnesemia and hypocalciuria were present.

We now know that BS defined genetically by an autosomal recessive transmission characterized by hypokalemic alkalosis with salt wasting, is a heterogenous group of disorders with at least two subsets, 'true' BS or 'classical' BS and GS. Each syndrome represents a distinct clinical, biochemical and molecular entity.

BS is caused by defects in the ion transportation system in the thick ascending limb of Henle's loop. Mutations of both genes which encode the renal chloride channel (C1C-Kb)[8] and the bumetadine-sensitive Na-K-2Cl co-transporter (NKCC2) have been identified[9]. In BS urinary calcium excretion is normal or high and serum magnesium levels are also normal. The syndrome is usually diagnosed in infancy or childhood, usually under the age of five. It is characterized by dehydration, polyuria, growth retardation and nephrocalcinosis.

GS is thought to be more common than BS. In 1996 Simon et al[1] first demonstrated complete linkage of GS with the SLC12A3 gene located on chromosome 16 (16q13) and consisted of 26 exons. This association has also been confirmed by other investigators[10]. Most of the genetic abnormalities identified in GS are missense mutations localised within the intracellular domains of the molecule protein which cause loss of activity of the sodium-chloride co-transporter (NCCT). As a result, increased sodium and chloride wasting in the distal convoluted tubule causes volume contraction. The hypovolemia activates the renin–angiotensin–aldosterone system and increases the secretion of potassium and hydrogen ions in the collecting duct.

The typical laboratory findings, apart from hypokalemic alkalosis, are hypomagnesemia and normocalcemic hypocalciuria[1,4]. The presence of these biochemical results distinguishes GS from BS. The electrolyte disturbances resemble the effects of chronic thiazide administration. Patients with GS are usually diagnosed in older age (adolescence or adulthood) during routine investigation. They are often asymptomatic or have intermittent mild symptoms that include muscular weakness, fatigue, cramps, occasional episodes of tetany, constipation, abdominal pain and vomiting[3,4]. The prognosis is usually benign and life expectancy is really high.

Treatment of GS consists of oral supplementation of magnesium and potassium. Magnesium therapy not only corrects the hypomagnesemia but also improves the hypokalemia. A potassium-sparing diuretic or a combination with anti-aldosterone medication and prostaglandin inhibitors may also be used.

Our patient presented with no severe symptoms. She was incidentally found to have hypokalemia. Laboratory data showed hypomagnesemia and hypocalciuria as well. Our suspicion of GS was confirmed after molecular analysis was done, which in our knowledge is the first case genetically identified in Greek population.

Table 1 shows the compared features between BS and GS and the specific findings identified in our patient.

We conclude that GS is a disorder with a variable symptom profile, but can be suspected on clinical and biochemical signs already in childhood. Unexplained hypokalemia may be caused by renal tubular disorders, such as GS. Electrolyte analysis and hormone evaluations are mandatory for differential diagnosis. Genetic analysis will further confirm the diagnosis.

Table 1: Features of Bartter and Gitelman syndrome.

	Bartter	Gitelman	our patient
Clinical findings			
Dehydration	+	–	–
Growth retardation	+	–	–
Polyuria	+	–	–
Weakness, cramps	–	+	–
Constipation	–	+	–
Abdominal pain	–	+	–
Biochemical findings			
Metabolic alkalosis	+	+	+
Hypokalemia	+	+	+
Hypomagnesemia	–	+	+
Hypocalciuria	–	+	+
Genetic analysis			
Renal defect	thick ascending Henle's loop	distal convoluted tubule	distal convoluted tubule
Mutation	C1C-Kb, NKCC2	NCCT	NCCT

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