A rare case of Gitelman’s syndrome presenting with hypocalcemia and osteopenia

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ABSTRACT. Gitelman’s syndrome (GS), an autosomal recessive disorder caused by a defect of the thiazide-sensitive Na-Cl cotransporter (TSC) at the distal tubule, is characterized by hyperreninemic hyperaldosteronism with normal or low blood pressure, hypokalemia, metabolic alkalosis, hypomagnesemia and hypocalciuria. An 18-yr-old Japanese man was admitted to our hospital with a history of muscle weakness and transient tetanic episodes. He showed hypocalciuria in addition to hypokalemia, severe hypomagnesemia, hypocalciuria and hyperreninemic hyperaldosteronism with normal blood pressure. Furthermore, bone mineral density at the lumbar spine revealed osteopenia. A diagnosis of GS was made on the basis of clinical features, laboratory data and renal function test. The electrolyte imbalance was corrected and bone mineral density was slightly increased with chronic treatment of magnesium and potassium salts. Genetic analysis revealed that TSC gene of the patient has a heterozygous C to A nucleotide substitution at position 545 in exon 4, which causes a threonine (Thr) to lysine (Lys) substitution at position 180. This is a rare case of GS with hypocalcemia and osteopenia which could be caused by severe hypomagnesemia.

INTRODUCTION

Gitelman’s syndrome (GS), recognized as a variant of Bartter’s syndrome (BS), is characterized by hypokalemic metabolic alkalosis in combination with hypomagnesemia, hypocalciuria and onset in early adulthood (1). GS is a homogenous distal tubular disorder caused by mutation of the thiazide-sensitive Na-Cl cotransporter (TSC) gene (2). To date, more than 100 distinct TSC mutations have been identified. Frequently, assessments of urinary calcium excretion and serum levels of magnesium are biochemical hallmarks to differentiate GS from BS (3). Although GS and BS, in general, have normal serum calcium levels, BS typically shows normal or increased calcium urinary excretion and GS is characterized by hypocalciuria (3). However, there are studies concerning calcitropic hormone metabolism in both conditions (5). One third of the patients with BS have hypomagnesemia, whereas most patients with GS have hypomagnesemia (3, 4). Therefore, overlapping of biochemical parameters has been observed (6, 7). Furthermore, recent reports stated that mutation in the kidney-specific basolateral Cl- channel gene, CLCNKB, also causes a mixed phenotype of GS and BS (8, 9). We report an unusual case of GS with hypocalcemia and osteopenia. The serum calcium levels were normalized by prescribing magnesium oxide and potassium gluconate.

CASE REPORT

An 18-yr-old Japanese man was admitted to our hospital with a history of muscle weakness and transient tetanic episodes in May 2003. He had not taken any regular medications including laxatives and diuretics. His parents were not consanguineous.
On physical examination, height was 164.3 cm and weight 68.6 kg. Blood pressure was 128/78 mmHg, and pulse rate was regular at 80/min. There were no abnormal signs such as Trousseau’s and Chvostek’s signs. Laboratory data are shown in Table 1. Severe hypomagnesemia, hypocalciuric hypocalcemia and hyperphosphatemia in addition to hypokalemia with hyperreninemic hyperaldosteronism were observed. Serum creatinine and creatinine clearance were normal. There was no evidence of inability of urinary concentrating. Intact PTH level was inappropriately low for hypocalcemia. The 1,25(\(\text{OH}\)\(_2\))\(\text{D}_3\) level was normal. Bone mineral density (BMD) at the lumbar spine (L2-L4) revealed osteopenia (BMD L2-L4: 0.661 g/cm\(^2\), T score; 74%). Brain and abdominal computerized tomography showed no abnormalities.

Since the severe electrolyte imbalance seemed to be attributed to GS despite the presence of a marked hypocalcemia, the renal clearance test using furosemide or thiazide was done according to described protocol (10). Distal fractional chloride reabsorption (\(\text{CH}_2\text{O}/\text{CH}_2\text{O}+\text{CCI})\) was markedly decreased by furosemide administration (from 77.7 to 19.4%), whereas thiazide administration had a minor effect on this parameter (85.2 to 75.7%).

The final diagnosis of GS was made on the basis of clinical features, laboratory data and renal clearance test. The clinical course is shown in Figure 1. After oral administration of magnesium oxide (0.5 g/day) and potassium gluconate (9.0 g/day), the electrolyte balance improved and his symptoms disappeared completely. The serum concentration of intact PTH was not altered but BMD was slightly increased after six months of medication.

Genetic analysis was made following the approval of the institutional review board and written informed consent by the patient and his family. TSC gene is composed of 26 exons. Using genomic DNA extracted from peripheral blood mononuclear cells, these exons were amplified by polymerase chain reaction (PCR) and PCR products were directly sequenced. Primers used and PCR conditions are described in a previous report (11). Direct sequence analysis revealed that the TSC gene of the patient has a heterozygous C to A nucleotide substitution at position 545 in exon 4 (Fig. 2). This mutation causes a threonine (Thr) to lysine (Lys) substitution at position 180. No other mutations on another allele were identified. Family analysis demonstrated that his father has the same mutation as the patient; however his mother and sister did