INTERNAL MEDICINE

□ CASE REPORT □

A Case of Gitelman Syndrome Associated with Idiopathic Intracranial Hypertension

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Abstract

An 18-year-old woman with Gitelman syndrome (GS) associated with idiopathic intracranial hypertension (IIH) is described. She was obese and showed a 10 kg gain in body weight over a period of 8 months. She presented with headache, vomiting, and diplopia. She had bilateral papilledema, and right abducens palsy. CSF examination demonstrated high pressure (over 320 mmH_2O) with normal cytochemistry. Brain MRI was normal. She showed mild alkalosis, hypokalemia, hypomagnesemia, increased plasma renin activity, and normal blood pressure. Two heterozygous mutations in the *SLC12A3* gene were identified. Therefore, she was diagnosed as GS with IIH. We should keep in mind the possible occurrence of IIH in GS.

Key words: idiopathic intracranial hypertension, Gitelman syndrome, *SLC12A3* gene

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Introduction

Gitelman syndrome (GS) is an autosomal recessive disorder characterized by hypokalemia caused by renal potassium wasting associated with metabolic alkalosis, hypomagnesemia, and normal otherwise renal function (1, 2). This disease is caused by an inactivating mutation in the *SLC12A3* gene coding thiazide-sensitive Na-Cl cotransporter (TSC) located on chromosome 16q13 (2-5). TSC is expressed specifically in renal distal convoluted tubule, where it mediates the reabsorption of Na^+ and Cl^-. GS is considered a mild type of the salt-losing tubular disorder, and most patients demonstrate mild symptoms such as muscle weakness, tetany, abdominal pain, paresthesia of the face and limbs, and some patients remain completely asymptomatic until electrolyte abnormalities are detected on routine evaluation in adulthood (1, 2).

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a disorder of elevated intracranial pressure due to an unknown cause. Patients manifest headache, visual blurring, papilledema with associated visual loss and diplopia due to abducent nerve palsy. Many etiological factors including drug side effects, and endocrinological and hematological diseases have been proposed (5-12). We report here a patient with GS associated with IIH.

Case Report

An 18-year-old woman presented with headache and left tinnitus at the same time. Six days later, she reported vomiting, and diplopia on looking to the right side. As her symptoms showed deterioration, she was admitted to our hospital. The nature of headache started as continuous head heaviness, and gradually deteriorated. She also presented with posterior neck pain on flexion. She was treated with oral administration of acetaminophen, but there was no improvement. She had no particular past history except for taking oral contraceptives a few times 6 months earlier. She had always had irregular menstrual periods, but had never been pregnant. Her parents were not consanguineous. Her perinatal period was unremarkable and psychomotor development was normal. On general physical examination, she was obese with a weight of 72 kg and height of 160 cm (BMI:

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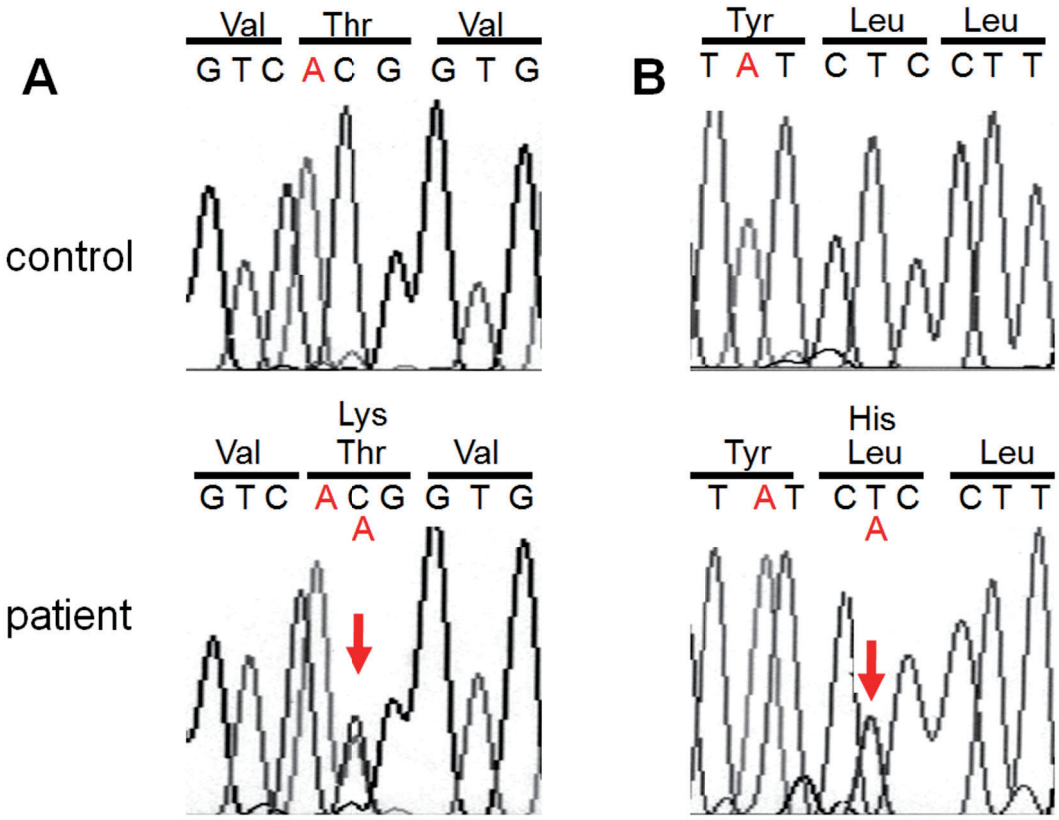

Figure 1. **Gene Analysis of the *SLC12A3*. Mutational analysis of the *SLC12A3* gene was performed in the control (top) and a patient (bottom) by the method of PCR direct sequencing method. A is exon 4, and B is exon 22. The mutation site is shown by an arrow. Two heterozygous mutations were identified in this patient. Heterozygous transitions of C to A at nucleotide 539 resulting in a Thr to Lys substitution at amino acid 180 (A), and heterozygous transitions of T to A at nucleotide 2546 resulting in a Leu to His substitution at amino acid 849 (B) were found.**

28.1). She had gained 10 kg of body weight in the previous 8 months. Her blood pressure was normal (114/53 mmHg), and there was no polydipsia, polyposia, or polyuria. Consciousness was alert with normal mentality. Neurological examination showed bilateral papilledema, and right abducens palsy. She showed slight neck stiffness and pain on neck flexion, but Kernig sign was negative. As CSF pressure was definitely elevated (over 320 mmH_2O), only 2 mL of CSF was collected. All cytochemical findings were normal. Brain enhanced MRI did not show any findings that could explain papilledema, such as mass lesion, cerebral venous thrombosis, and thickness of the dura. As the underlying causes of increased intracranial CSF pressure could not be found, she was diagnosed as having IIH based on the Modified Dandy Criteria (9). Her headache was classified as headache attributed to IIH, ICHD II code 7.1.1.

Routine hematological studies, urinalysis, serum protein, serum creatine and creatinine, serum cholesterol and lipids, fasting blood sugar, and serum serologic reactions were all normal or negative. Serum potassium (3.3 mEq/L) and magnesium (1.9 mg/dL) levels were mildly decreased. Other electrolytes including calcium were all normal. Urinary potassium excretion was preserved (41 mEq/day, normal; 25-125 mEq/day). Urinary calcium (45.5 mg/day, normal; 100-300 mg/day) and magnesium excretion (30.3 mg/day, normal; 50-200 mg/day) was decreased. Arterial blood pH showed mild alkalosis (pH 7.46). Renal, hepatic, thyroid and parathyroid functions were all normal. Vitamin A level was normal. Plasma renin activity was definitely elevated (15.9 ng/mL/hr, normal; 0.2-3.9), but aldosterone was only mildly elevated (160.0 pg/mL, normal; 35-159 pg/mL). Abdominal CT did not show any adrenal tumors. These findings strongly suggest that the patient had GS or an atypical type of Bartter syndrome.

Genetic analysis

Genetic analysis was performed written informed consent was obtained from the patient and her parents. Total DNA was extracted from blood peripheral leukocytes. Mutational analysis of the *SLC12A3* gene was examined by PCR direct sequencing and PCR-RFLP methods, as previously reported (4). Two heterozygous mutations were identified in this patient. One heterozygous mutation was T180K in exon 4, and another was L849H in exon 22 (Fig. 1). Thus, the patient demonstrated compound heterozygosity in the *SLC12A3* gene. These mutations were previously identified in Japanese GS patients.

Treatment and clinical course

The day after the first CSF examination, her headache disappeared. The patient was treated by intravenous infusion of glycerin for 13 days. Additionally, diet therapy was undertaken. She gradually lost about 2 kg of body weight per month. Potassium and magnesium levels increased to within the normal range. Within a month, diplopia and papilledema had completely disappeared. Follow-up CSF examined 11 days later showed still high pressure (300 mmH_2O). Laboratory data examined 7 days after the first examinations were as follows: urinary potassium excretion 20.5 mEq/day, and calcium excretion 40.17 mg/day. Arterial blood pH showed mild alkalosis (7.462). Plasma rennin activity was high (8.1 ng/mL/hr), but aldsterone was normal (112.0 pg/mL). She was followed up one and half years. There was no recurrence of the symptoms suggestive of IIH.

Discussion

The present patient showed biochemical abnormalities including hypokalemia, with metabolic alkalosis, hypomagnesemia, low excretion of urinary calcium, and increased plasma renin activity, which strongly suggest GS or an atypical form of Bartter syndrome (1, 2). Mutation of *SLC12A3* gene was detected, and the diagnosis of GS was confirmed.

In general, many patients with GS show minor or mild symptoms such as fatigue, weakness, salt craving, or cramp, and some patients even remain completely asymptomatic (1, 2). However, the present patient showed neurological manifestations and a clinical course compatible with IIH. To our knowledge, there is one previous report of GS (5) and three reports of Bartter syndrome (10-12) associated with IIH in the literature. As for etiological factors of IIH, drug side effects, endocrinological and hematological diseases have been reported. Some possible pathophysiological and pathogenic causes of IIH have been proposed, including decreased CSF absorption by the arachnoid villi, venous intracranial hypertension, increased cerebral volume or increased CSF production by the choroid plexus (6-9). In cases of GS or Bartter syndrome, it was suggested that electrolyte abnormalities and secondary aldosteronism may play a role in inducing IIH (5).

The choroid plexus in the CNS has a high-affinity aldosterone-receptor binding site, which is involved in the production of CSF. Aldosterone is actively involved in producing CSF volume and composition, as well as in the regulation of blood pressure. As the renin- aldosterone system is activated in GS, aldosterone levels in the CSF as well as in plasma will increase, and stimulate the net transport and reabsorption of sodium/potassium across the epithelium in the choroidal plexus, and thus may be involved in the increased production of CSF (5, 13).

IIH is more common in women and obese individuals. The reported female to male ratios range from 4-15:1, and published frequencies of obesity are 71-94% (7). Obesity leads to increased intra-abdominal pressure, which increases intrathoracic and intracerebral venous pressure, resulting in increased intracranial pressure. It is also suggested that the excessive conversion of androstenedione to estrone by adipocytes in obese patients may favor excessive brain water (6-9). In the present patient, symptoms were markedly improved by diet therapy. Obesity was apparently a major factor promoting IIH in our case. Additionally, she had always had an irregular menstrual period, and took oral contraceptives a few times. It was suggested that these factors were also risk factors to induce IIH. Actually, in our patient, the aldosterone level was only mildly elevated on the first examination, but follow-up study showed a normal level. Thus, the accumulation of these risk factors, i.e. obesity, female, menstrual irregularity, oral contraceptives, and association with GS, probably contributed to inducing IIH in this patient.

More than 140 different *SLC12A3* mutations have been identified. The T180K and L849H mutation alleles identified in the present patient, are frequently seen in Japanese GS patients (14). There was no correlation between the position or nature of the mutation in *SLC12A3* and the severity of clinical manifestations (15). In fact, another patient with GS and IIH (5) showed a different mutation of *SLC12A3* than that of our patient.

GS is generally a disorder showing minor or mild symptoms, and its long-term prognosis is also excellent. However, this disorder has an additional endogenous etiological factor to induce IIH. We should keep in mind that a critical association with IIH may occur in patients with GS.

The authors state that they have no Conflict of Interest (COI).

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