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A novel mutation in *KCNJ1* in a Bartter syndrome case diagnosed as pseudohypoaldosteronism

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Abstract

Bartter syndrome (BS) is a genetic disorder with hypokalemic metabolic alkalosis and is classified into five types. One of these, Type II BS (OMIM: 241200), is classified as a neonatal Bartter syndrome, which is caused by mutations in the *KCNJ1* gene. Transient hyperkalemia and hyponatremia are usually noted in the early postnatal period, however, type II BS is a relatively rare disease, so that the exact clinical course or the genetic background of this disease has not yet been well characterized. This report concerns a male type II BS patient with a novel mutation in the *KCNJ1* gene. He was diagnosed with pseudohypoaldosteronism (PHA) in the early neonatal period because of hyperkalemia (8.9 mEq/L), hyponatremia and metabolic acidosis. In adolescence, he shows normal potassium level without undergoing any treatment. His renal function is normal but shows hypercalciuria and nephrocalcinosis. Genetic analysis of the *KCNJ1* gene identified the novel homozygous 1 bp deletion mutation (c.607 del C in exon 5). Our case shows unique clinical findings that in early postnatal period he showed hypokalemia and metabolic acidosis diagnosed as PHA and in adolescent period he showed hypercalciuria and nephrocalcinosis with normal potassium levels without any treatment. In such a case, we should suspect *KCNJ1* mutations. Introduction

Bartter syndromes (BS) are inherited disorders characterized by hypokalemic metabolic alkalosis accompanied by normal or low blood pressure despite hyperreninemia and hyperaldosteronemia. Recent genetic studies have found that these diseases are caused by mutations, which lead to transporter or channel loss-of-function directly or secondary, in five genes. The first gene is the *SLC12A1* gene, which encodes the apical Na-K-2Cl cotransporter (NKCC2); the second is the *KCNJ1* gene, which encodes the apical renal outer medullary K channel (ROMK); the third is the *CLCNKB* gene, which encodes the basolateral Cl channel Kb (ClC-Kb). The mutations of these genes lead to type I-III BS respectively [1-4]. In recent years, the

fourth gene, *BSND* coding barttin, a subunit for ClC-Ka and ClC-Kb, has been identified as responsible for a combination of antenatal BS and sensorineural deafness and a phenotype now known as type IV BS [5]. Finally, a coding gene called *CASR* has been identified as causing type V BS, which is associated with hypoparathyroidism and due to a gain of function mutations in the calcium sensing receptor [6,7].

Patients with type I and type II BS are characterized by impaired renal concentrating capacity, saliuretic polyuria and hypercalciuria leading to the clinical characteristics of polyhydramnios, hypo- or isosthenuria and nephrocalcinosis. These signs are believed to clearly differentiate these patients from those with type III BS and they have therefore been classified as antenatal BS. In contrast to type I BS patients, type II patients usually show transient neonatal hyperkalemia, hyponatremia and some of them also transient metabolic acidosis. Moreover, type II BS cases show milder renal potassium loss and have minimal-to-normal hypokalemia compared with type I BS [8].

This report describes a patient with type II BS who showed transient hyperkalemia, hyponatremia and metabolic acidosis and who was diagnosed with pseudohypoaldosteronism (PHA) in the neonatal period but in adolescence showed normal potassium levels without undergoing any treatment.

Discussion

This report describes a patient with neonatal BS accompanied by severe hyperkalemia, hyponatremia and metabolic acidosis evident in the early neonatal period, who was initially diagnosed with PHA. In childhood, however, he showed mild hypokalemia, which became normal in adolescence when hypercalciuria and nephrocalcinosis were observed. Genetic analysis detected a homozygous 1 bp deletion mutation (c.607 del C in exon5) in the *KCNJ1* gene, so that this patient's disease was diagnosed as type II BS (OMIM 241200).

Some authors have reported that the majority of patients with type II BS show hyperkalemia and hyponatremia and that some of them show metabolic acidosis in the early neonatal period [10]. After the neonatal period, serum potassium levels are less depressed than in type I BS, even though most of the previously reported type II BS patients were taking indomethacin [8,10]. Jeck et al. reported that of ten patients with type II BS, three showed signs of transitory and marked hyperkalemia in the neonatal period and two of them did not show hypokalemic alkalosis at any time [8]. Peters et al. reported that 9 of 14 patients had hyperkalemia and that the younger the gestational age is, the higher the maximal serum potassium level is likely to be and that the patients showed no transitory hyperkalemia after 32 weeks of gestation. They demonstrated that there was a significant negative correlation between gestational age and maximal serum potassium. Moreover, 3 of their patients were suspected of having PHA [9]. Finer et al. reported on 12 cases with hyperkalemia, whose plasma potassium levels peaked generally at the third day of life and gradually decreased to normal values. One of them died of ventricular arrhythmias with a peak potassium level of 10.5mEq/L. In addition, they reported that, although normal potassium levels were observed in some of the patients during childhood, most of them were taking indomethacin [10]. Premature neonates usually have a higher baseline plasma K level that is suggested to contribute to decreased Na-K-ATPase activity. Landau states in a review article that transient hyperkalemia may attributed to gestational-age-related decreased Na-K-ATPase activity. This transient hyperkalemia would then be resolved as the transporter activity becomes elevated during postnatal maturation [11]. On the other hand, urinary K excretion is derived almost entirely from K secretion in the connecting tubule and cortical collecting duct (CCD) [12]. In contrast to the high rates of K secretion observed in CCDs isolated from adult animals neonatal animals show no significant K transport until 3 weeks of gestation and these results indicate that the low rates of urinary K secretion characteristic of the newborn kidney are due, at least in part, to a

low secretory capacity of the CCD [13]. It has been reported by several authors that an increase in tubular fluid flow rate in CCD stimulates K secretion [reviewed in 14]. Woda et al. reported that the absence of flow-dependent K secretion early in life is due to the developmental regulation of expression of maxi-K channel [15]. The K retention characteristic of the neonatal kidney is due, in part, to a paucity of flow-stimulated K secretion in the CCD. Thus, in addition to loss of ROMK channel function and decreased Na-K-ATPase activity, low expression of maxi-K channel may lead to the severe transient hyperkalemia seen in type II BS.

In infantile period, patients with type II BS develop hypokalemia owing to increased renal potassium excretion. The reason has been believed that loss of function in ROMK channel activity in the thick ascending limb (TAL) may leads to the inactivation of NKCC2. Recently, Baily et al. reported that this renal potassium loss in type II BS patients is due to both reduced reabsorption in the TAL and K secretion by maxi-K channels in the late distal tubule which were confirmed using ROMK-deficient mice [16]. In this way, maxi-K channel may considerably contribute to this unique clinical course of type II BS.

The *KCNJ1* gene is thought to produce several isoforms of ROMK. Exon5 is common to all of these isoforms and encodes the majority of the channel proteins [17]. Mutations in exon5 may therefore cause the transient hyperkalemia in the early neonate period or milder serum electrolyte abnormality after the neonatal period compared with that in type I BS. The mutation identified in this patient was homozygous 1 bp deletion that makes the frame shift from 203 amino acid (aa). This mutation would lead to the dysfunction in the ATP-binding regulatory domain (aa190-240) and C-terminus. Several point mutations in this area have already reported and clearly explained the mechanism leading to ROMK dysfunction. The ATP-binding regulatory domain may abolish protein kinase A (PKA) phosphorylation that was found to lower the affinity for phosphatidylinositol

lipids and decline the channel open probability [18, 19]. Mutations in the C-terminus have reported to change the structural arrangement of the pH sensor and shift the pH gating to more alkaline pH values [20].

Our case is now 18 years old. Appearance and intelligence are normal and height is almost normal. He shows a normal potassium level, mild alkalosis, hypercalciuria and nephrocalcinosis. He has never received any treatment and after childhood, clinical course was very mild. Our case shows novel clinical findings that in early postnatal period he showed hypokalemia and metabolic acidosis diagnosed as PHA and in adolescent period he showed hypercalciuria and nephrocalcinosis with normal potassium levels without any treatment.

In conclusion, we should be aware of the possibility of this unusual course of type II BS and perform genetic analysis to confirm whether suspicion of type II BS is warranted.

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Fig. 1

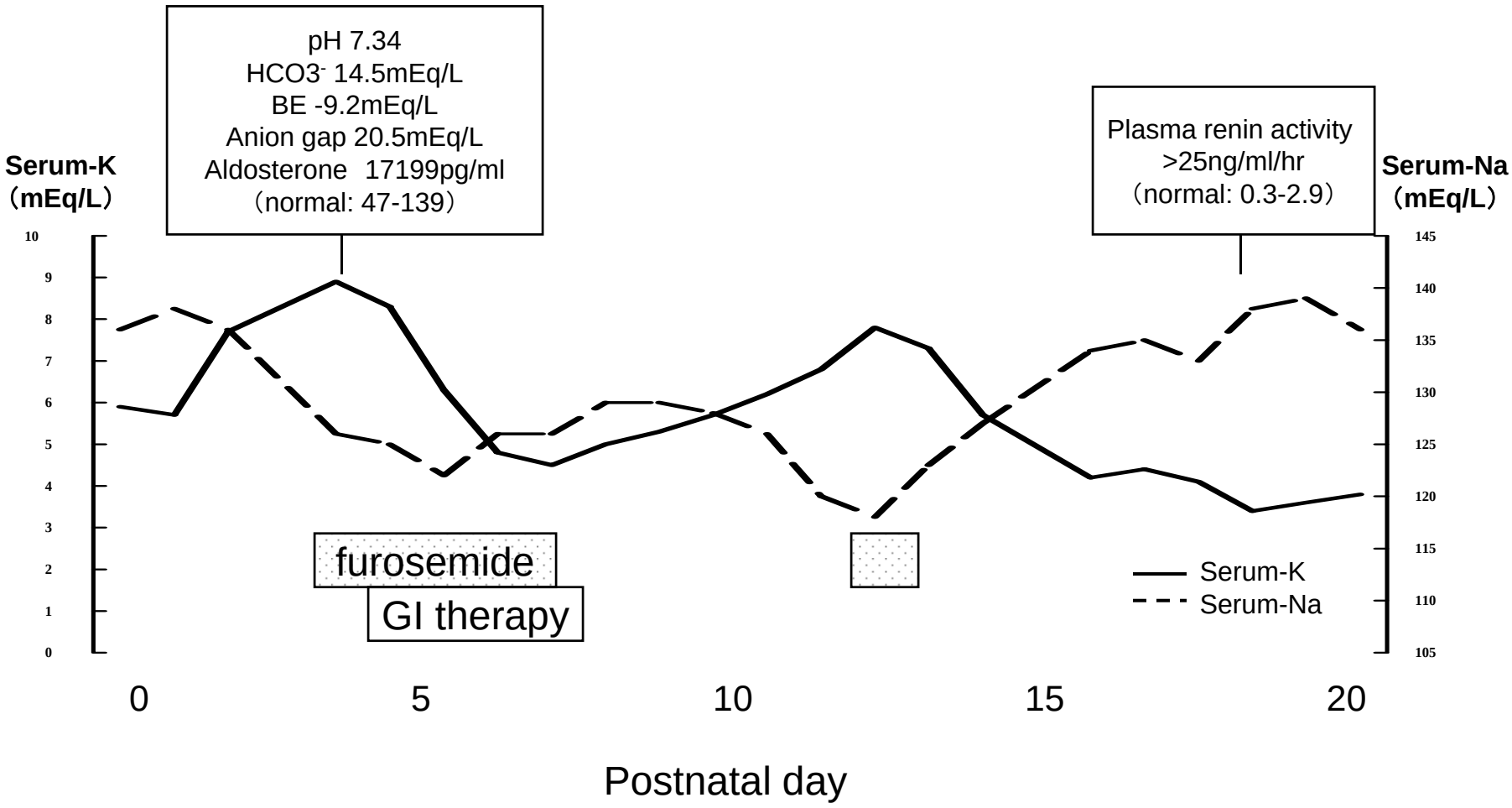
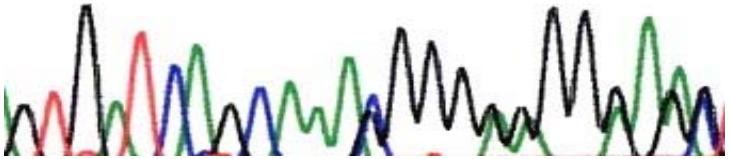

pH 7.34
HCO3- 14.5mEq/L
BE -9.2mEq/L
Anion gap 20.5mEq/L
Aldosterone 17199pg/ml
（normal: 47-139）
Plasma renin activity
>25ng/ml/hr
（normal: 0.3-2.9）
Serum-K
（mEq/L）
Serum-Na
（mEq/L）
10
9
8
7
6
5
4
3
2
1
0
145
140
135
130
125
120
115
110
105
furosemide
GI therapy
Serum-K
Serum-Na
0
5
10
15
20
Postnatal day

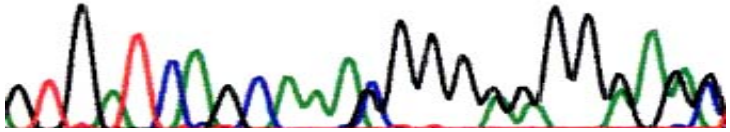
Fig. 2

Father



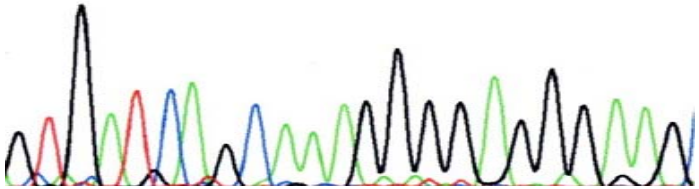
Wild type: GTG ATC AGC AAA CGG GGA GGG AAG
Mutant : GTG ATC AGC AAA GGG GAG GGA AGC

Mother



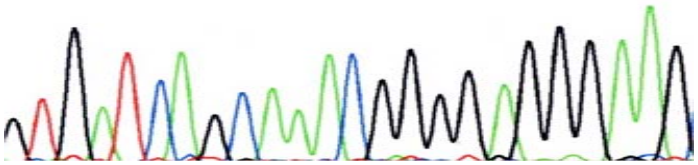
Wild type: GTG ATC AGC AAA CGG GGA GGG AAG
Mutant : GTG ATC AGC AAA GGG GAG GGA AGC

Patient



GTG ATC AGC AAA GGG GAG GGA AG

Normal



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