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BRIEF REPORT

Early appearance of hypokalemia in Gitelman syndrome

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Abstract Inactivating mutations in the *SLC12A3* gene that encodes the thiazide-sensitive co-transporter causes Gitelman syndrome. The main features of this syndrome include normal or low blood pressure, hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria, and hyperreninemia. These patients are at low risk for preterm birth and do not present with symptoms before school age. As a consequence, the condition is usually diagnosed in late childhood or in adult life. We report on four patients, two pairs of prematurely born twins, in whom hypokalemia was demonstrated early in life. In these children, a tendency towards hypokalemia was first noted during the third week of life. Overt hypokalemia subsequently appeared associated with normal blood pressure, hypochloremia, hyperreninemia, and an inappropriately high fractional excretion of potassium and chloride. Molecular biology studies failed to detect mutations in the *SLC12A1*, *KCNJ1*, and *CLCNKB* genes responsible for the Bartter syndromes type I, II and III, respectively. Compound heterozygous mutations in the *SLC12A3* gene were detected in both pairs of twins: a frameshift mutation in exon 10 (c.1196_1202dup7bp), leading to the truncated protein p. Ser402X, and a missense mutation in exon 11, p.Ser475Cys (c.1424C>G) in the first pair; two missense mutations, p. Thr392Ile (c.1175C>T) in exon 9 and p.Ser615Leu in exon 15 (c.1844C>T), in the second pair. In conclusion, the diagnosis of Gitelman syndrome deserves consideration in infants with unexplained hypokalemia.

Keywords Gitelman syndrome · Bartter syndrome · Hypokalemia · Hypomagnesemia · Preterm neonate

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Introduction

Inactivating mutations in the *SLC12A3* gene that encodes the thiazide-sensitive sodium chloride co-transporter cause Gitelman syndrome (OMIM 263800), an autosomal-recessive renal tubular disorder whose features include hypokalemia, metabolic alkalosis, hypomagnesemia, hypocalciuria, secondary hyperreninemic aldosteronism, and normal or low blood pressure [1–4]. These patients are at low risk for preterm birth and do not present symptoms (transient periods of tetany or muscle weakness, abdominal

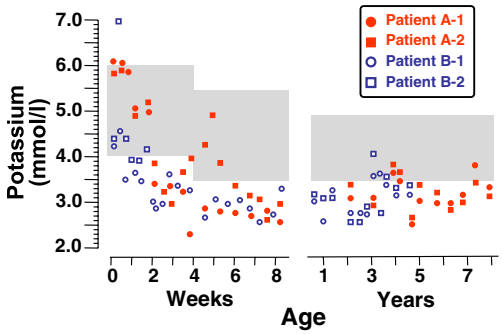

Fig. 1 Plasma potassium levels in two pairs of prematurely born twins (*A-1*/*A-2* and *B-1*/*B-2*, respectively) with Gitelman syndrome. *Shaded frame* Reference values

pain, and vomiting) before school age. As a consequence, the condition is generally not diagnosed until late childhood or even adulthood [1–4].

We report on four Gitelman patients, two pairs of prematurely born twins, in whom hypokalemia was demonstrated very early in life.

Case reports

Family A

This pair of male twins was born after 28 weeks of gestation to a mother with a monochorionic, monoamniotic placenta, twin-to-twin transfusion, and normal level of amniotic fluid.

The first twin (patient A-1) was born with a body weight of 0.655 kg. He presented with severe respiratory distress syndrome, severe anemia, periventricular white matter injury, and signs of neonatal infection and was treated with mechanical ventilation, red blood cell transfusion, and various antimicrobials (ampicillin, aminoglycosides, vancomycin and third generation cephalosporins). Following an initial, mild, and self-remitting tendency to hyperkalemia (elevation 6.1 mmol/l; Fig. 1, left panel), mild hyponatremia (129 mmol/l) and hypokalemia (3.4 mmol/l) were first observed at age 17 days. However, the tendency towards hypokalemia (and hyponatremia) persisted despite supplementation with potassium chloride (up to 9.0 mmol/kg body weight daily). Both plasma renin activity (7.9 ng/ml h; institutional reference values 0.2–2.7 ng/ml h) and aldosterone (520 ng/l; reference 50–150 ng/l) were subsequently found to be increased. Findings on the renal echography were normal.

At the age of 2 years, normal blood pressure, persisting hypokalemia (3.1 mmol/l), inappropriately high urinary potassium (fractional excretion 72.1×10^{-2}; reference: $\leq15.0\times10^{-2}$) and chloride (fractional excretion 2.65×10^{-2}; reference $\leq1.00\times10^{-2}$) excretion, hyperreninemia (3,200 ng/l; institutional reference value 150–300 ng/l), hyperaldosteronism (270 ng/l) and hypocalciuria (urinary calcium/creatinine ratio <0.01 mol/mol) were noted. The subsequent follow-up (Fig. 1, right panel) confirmed the tendency towards chronic hypokalemia and revealed the development of hypomagnesemia from the age of 41 months (Fig. 2).

The second twin (patient A-2), who was born with a weight of 1.410 kg, developed a mild respiratory distress syndrome and signs of neonatal infection. He was treated with ampicillin, aminoglycosides, and a third generation cephalosporin. Hypokalemia (2.8 mmol/l), hypochloremia (85 mmol/l), hyperreninemia (plasma renin activity > 50 ng/ml h) and hyperaldosteronism (1,506 ng/l) were first observed during the third week of life (Fig. 1, left panel). Normal blood pressure, persisting mild hypokalemia (3.4 mmol/l), hypocalciuria (urinary calcium/creatinine ratio <0.03 mol/mol), an inappropriately high urinary potassium (fractional excretion 41.9×10^{-2}) and chloride (fractional excretion 3.06×10^{-2}) excretion, hyperreninemia (1,190 ng/l), and hyperaldosteronism (226 ng/l) were noted at the age of 2 years. The findings on the renal echography were normal. The subsequent follow-up (Fig. 1, right panel) confirmed the tendency towards chronic hypokalemia and demonstrated the development of hypomagnesemia from the age of 4 years (Fig. 2).

At that time, both children were put on a treatment with indomethacin. The plasma potassium values subsequently ranged between 2.5 and 3.8 mmol/l in both children (Fig. 1, right panel). At last follow-up, the children were 7.5 years old. They were being treated with potassium chloride, 1.0 mmol/kg body weight daily, sodium chloride, 1.0 mmol/kg body weight daily, and indomethacin, 0.7 mg/kg body weight daily. Their weight and height Z score were −1.59 and −3.17 for the first twin and +0.63 and −0.55 for the second twin, respectively.

Family B

This pair of female twins was born after 34 weeks of gestation to a mother affected by pre-eclampsia with a monochorionic, diamniotic placenta and normal level of amniotic fluid.

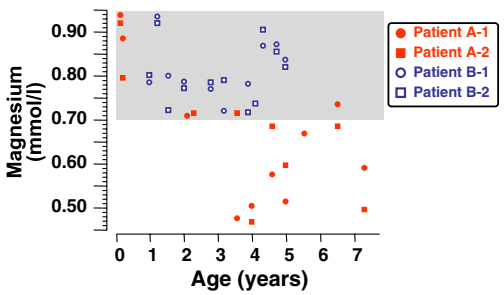

Fig. 2 Total plasma magnesium levels in two pairs of prematurely born twins with Gitelman syndrome. *Shaded frame* Reference values

The first baby (patient B-1), who had a low-normal gestational age body weight of 1.520 kg, presented with hypoglycemia, which was managed with intravenous glucose, apnea of prematurity, which was managed with oral caffeine, and anemia, which was managed with iron and recombinant erythropoietin. Hyponatremia (126 mmol/l), hypochloremia (86 mmol/l), hypokalemia (Fig. 1, left panel), and hyperbicarbonatemia (30.0 mmol/l), associated with hyperreninemia (1,800 ng/l) and hyperaldosteronism (625 ng/l), were first observed at the age of 15 days. As a consequence, oral supplementation with potassium chloride was initiated. At the age of 7 months, normal blood pressure, persisting hypokalemia (3.1 mmol/l; Fig. 1, right panel), inappropriately high urine potassium (fractional excretion 56.5×10^{-2}) and chloride (fractional excretion 3.23×10^{-2}) excretion, hyperreninemia (1,100 ng/l), and hyperaldosteronism (507 ng/l) were noted. The findings on the renal echography were normal.

The second twin (patient B-2) was born with a weight of 2.235 kg. She presented with a mild respiratory distress syndrome and transient, self-remitting hyperkalemia (Fig. 1, left panel) for 2 days. Circulating potassium and bicarbonate (from 21.1 to 22.6 mmol/l) were normal during the remaining hospital stay. At the age of 12 months, normal blood pressure, hypokalemia (3.2 mmol/l) (Fig. 1, right panel), inappropriately high urine potassium (fractional excretion 38.5×10^{-2}) and chloride (fractional excretion 1.80×10^{-2}) excretion, hyperreninemia (2,570 ng/l), and hyperaldosteronism (264 ng/l) were observed.

The plasma potassium values ranged between 2.6 and 4.1 mmol/l (Fig. 1, right panel) in both children when on medication with indomethacin (0.8 mg/kg body weight daily). No clear-cut tendency towards hypomagnesemia was noted (Fig. 2). At the last follow-up, the children were 5 years old. Medication was with potassium chloride, 3.0 mmol/kg body weight daily, sodium chloride, 1.5 mmol/kg body weight daily, and indomethacin, 1.0 mg/kg body weight daily. Their weight and height Z score were −1.61 and −0.44 for the first twin and −0.88 and +0.14 for the second twin, respectively. Their urinary calcium/creatinine ratio was persistently <0.021 mol/mol.

Molecular biology studies

The four children did not harbor mutations in the *CLCNKB* gene, the cause of classic Bartter syndrome, or in the *KCNJ1* and *CLCNKB* genes, the main causes of antenatal Bartter syndrome [5, 6]. However, compound heterozygous mutations were disclosed in the *SLC12A3* gene [3]. The first pair of twins (patients A-1 and -2) presents a frameshift mutation of paternal origin in exon 10 (c.1196_1202dup7bp), which leads to the truncated protein p.Ser402X, and a missense mutation of maternal origin in exon 11, p.Ser475Cys (c.1424C>G). The second pair carries two missense mutations: p.Thr392Ile (c.1175C>T) in exon 9 of maternal origin and p.Ser615Leu in exon 15 (c.1844C>T) of paternal origin.

Discussion

Gitelman syndrome is classically considered to be a rather benign condition that is not diagnosed until late childhood or even adulthood [4]. To the best of the authors' knowledge, this is the first report that documents hypokalemia in affected newborns.

The mutations identified in our second pair of twins (p.Ser615Leu and p.Thr392Ile) have already been reported in patients with the classical clinical and biochemical features of Gitelman syndrome [7, 8], suggesting that our two patients do not represent an unusual sub-form of this tubulopathy. Rather, we assume that the laboratory abnormalities serendipitously documented since late neonatal life in our prematurely born Gitelman children are representative of all patients affected with this renal tubular disorder. This hypothesis is supported by the case of a 5-month-old boy who developed severe cardiac arrhythmia in the context of acute diarrhea with a potassium level of 1.7 mmol/l. In this child, the clinical and molecular diagnosis of Gitelman syndrome was made some weeks after the episode in the context of persisting hypokalemia [9].

In our prematurely born Gitelman-babies, hypokalemia was not observed before the third week of life. This fact likely reflects the recognized tendency of premature newborns to have rather high circulating potassium values, which is a result of a blunted renal potassium excretion, as well as aldosterone unresponsiveness and potassium loss from the intra- into the extra-cellular space [10, 11].

Plasma renin values vary inversely with age in infancy [12]. Unfortunately, the values measured in our patients were compared with institutional reference values assessed in adults. This occasionally led to an overestimation of the recognized tendency to hyperreninemia noted in Gitelman syndrome.

Drugs prescribed to some of our prematurely born Gitelman-patients, including β-lactams, aminoglycosides and especially caffeine, may sometimes cause hypokalemia [13, 14]. The persistence of hypokalemia after the withdrawal of these drugs and the clear-cut results of genotype analysis indicate that the prescribed drugs played a relatively minor role in our patients as the cause of hypokalemia during early infancy.

Hypomagnesemia, a very characteristic laboratory feature in Gitelman syndrome, developed only during the fourth year of life in patients A-1 and A-2. In contrast,

blood magnesium levels were still normal at the last follow-up in patients B-1 and B-2.

Hypocalciuria, a very characteristic laboratory feature in Gitelman syndrome [2–4] can sometimes occur in classic Bartter syndrome [15]. Unfortunately, the urinary calcium excretion was assessed only after treatment initiation with indomethacin in two of our patients.

In conclusion, our clinical experience with these four patients suggests that the diagnosis of Gitelman syndrome deserves consideration in infants with unexplained hypokalemia, even if not associated with hypomagnesemia.

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