Clinical Course and Prognosis of Tubulopathies Characterized by Metabolic Alkalosis in Children

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What is already known on this topic?

- Bartter and Gitelman syndromes are rare inherited tubulopathies characterized by hypokalemic, hypochloremic metabolic alkalosis. The genotype and phenotype distribution of the patients differ according to the populations. Bartter and Gitelman syndromes can cause advanced chronic kidney disease and require lifelong follow-up and treatment.

What this study adds on this topic?

- We determined the frequency of the phenotypic and genotypic subgroups, clinical features, long-term management, and prognosis of children diagnosed with Bartter and Gitelman syndromes.
- Congenital anomalies of kidney and urinary tract are the most common cause of stage 5 chronic kidney disease in children in our country. This study shows that tubulopathies like Bartter syndrome also could cause advanced-stage chronic kidney disease in children.

ABSTRACT

Objective: Bartter syndrome and Gitelman syndrome are rare inherited tubulopathies characterized by hypokalemic, hypochloremic metabolic alkalosis. This study aimed to clarify the frequency of the phenotypic and genotypic subgroups, clinical features, long-term management, and prognosis of children diagnosed with Bartter syndrome and Gitelman syndrome in this study.

Materials and Methods: Twenty-seven patients with Bartter syndrome and 6 patients with Gitelman syndrome, who were followed up between 2004 and 2020 in a single center, were included in the study.

Results: The median age of diagnosis was 4 months in patients with Bartter syndrome and 174 months in patients with Gitelman syndrome. At the last follow-up, a total of 12 Bartter syndrome patients had chronic kidney disease with a mean 7.79 ± 4.73 years of age; 5 (18.5%) of these patients had chronic kidney disease stage 2, 5 (18.5%) had chronic kidney disease stage 3, and 2 (7.4%) had chronic kidney disease stage 5. Of the 5 patients with Bartter syndrome with chronic kidney disease stage 2, 2 had CLCNKB and 1 had SLC12A1 gene mutation. Also, CLCNKB mutation was detected in 2 of 5 patients with Bartter syndrome with chronic kidney disease stage 3. Finally, 2 patients with Bartter syndrome with chronic kidney disease stage 5 had BSND mutation in one and CLCNKB mutation in the other. Estimated glomerular filtration rates of all patients with Gitelman syndrome were normal at the last follow-up. There was no statistically significant association of development of chronic kidney disease with genetic mutation, nephrocalcinosis, prematurity, and hypokalemia.

Conclusion: Patients with Bartter syndrome and Gitelman syndrome may have a different clinical course due to the underlying genetic mutation. Bartter syndrome and Gitelman syndrome require lifelong treatment, and regular follow-up is important to prevent advanced-stage chronic kidney disease.

Keywords: Bartter syndrome, Gitelman syndrome, chronic kidney disease

INTRODUCTION

Bartter and Gitelman syndromes (BS and GS) are rare inherited tubulopathies characterized by hypokalemic, hypochloremic metabolic alkalosis. Patients with BS present with polyuria, hypokalemia, hypochloremia and metabolic alkalosis, normal blood pressure, and elevated renin–aldosterone levels.1 Two phenotypes exist in BS: antenatal BS and classical BS. Also, BS is classified genotypically into 5 subtypes as SLC12A1 (BS type 1), KCNJ1 (BS type 2), CLCNKB (BS type 3), BSND (BS type 4a), CLCNKA+CLCNKB (BS type 4b), and MAGED2 (BS type 5).2 Bartter syndrome types 1, 2, and 4 are classified as “antenatal Bartter syndrome” due to common presentation with polyhydramnios and prematurity. Congenital chloride-losing diarrhea should be considered in the differential diagnosis of infants with...
metabolic alkalosis, polyhydramnios, and a history of premature birth, and unlike BS, the diagnosis is made by showing stool chloride loss and the diagnosis is confirmed by genetic analysis. Furthermore, BS type 3 is termed “classical Bartter syndrome” because it typically occurs in late childhood and is closest to the disease described by Bartter.

Patients with GS typically present in late childhood with hypokalemia, hypochloremia and metabolic alkalosis, normal blood pressure, and hyperaldosteronism. GS is caused by mutation on SLC12A3 gene.

Since consanguineous marriages are common in our country, hereditary tubulopathies are frequently encountered. The clinical course of patients with BS and GS can be different. The presenting symptoms of children with BS and GS are dehydration episodes, fever, constipation/diarrhea, and growth retardation. Chronic kidney disease (CKD) progresses to kidney failure over the years in patients with BS and GS. Early diagnosis and treatment in these children can prevent possible complications. Little data on the clinical course and prognosis of the disease have been reported in the literature due to the rarity of BS and GS all over the world. This study aimed to evaluate the frequency of the phenotypic and genotypic subgroups, clinical features, long-term management, and prognosis of children diagnosed with BS and GS in the Çukurova region.

MATERIALS AND METHODS

Study Population
The present study includes 27 patients with BS and 6 patients with GS who were diagnosed and followed up between 2004 and 2020 in the Pediatric Nephrology Department of Çukurova University. Bartter syndrome was diagnosed in patients with hypokalemic, hypochloremic metabolic alkalosis, normal blood pressure, excessive urine losses of calcium and chloride and history of polyuria, polyhydramnios, and prematurity. Gitelman syndrome was diagnosed in patients with hypokalemic, hypochloremic metabolic alkalosis, hypomagnesemia, normal blood pressure, and hypocaliuria. The patients were phenotypically divided into 3 groups: antenatal BS, classical BS, and GS. The patients with genetic analysis results were also genetically divided into groups.

Study Procedure
The medical records of patients were retrospectively reviewed for data, including sex, age at diagnosis, presenting symptoms, growth parameters, duration of the follow-up period, biochemical results, molecular genetic analysis, and family history.

In blood biochemistry, blood urea nitrogen and creatinine were studied with the enzymatic–photometric (Beckman Coulter AU5800, Brea, CA, USA) method, while sodium, potassium, and chlorine were studied with the ISE (Beckman Coulter AU5800) method. Blood magnesium, calcium, and urinary calcium were studied by photometric (Beckman Coulter AU5800) method. Parathormone was studied with the CL (Beckman Coulter UniCel-Dxl) method. Urine creatinine was studied with alkaline picrate IF CC-IDMS standardized (Beckman Coulter AU5800) method. pH and HCO₃ value in blood gas were calculated using ABL800 FLEX. Renin and aldosterone were studied using the RIA (PerkinElmer Wizard II 2470) method.

Standard deviation scores (SDS) were expressed according to anthropometric references in Turkish children. The estimated glomerular filtration rates (eGFRs) of patients were calculated using the Schwartz formula. The Kidney Disease: Improving Global Outcomes guideline was used to define stages of CKD. Chronic kidney disease stage 1 is defined as an eGFR > 90 mL/min/1.73 m², CKD stage 2 is defined as an eGFR of 60–89 mL/min/1.73 m², CKD stage 3 is defined as an eGFR of 30–59 mL/min/1.73 m², CKD stage 4 is defined as an eGFR of 15–29 mL/min/1.73 m², and CKD stage 5 is defined as an eGFR < 15 mL/min/1.73 m².

This study was approved by the Ethical Committee of the Çukurova University Medical Faculty (04.10.2019–92/5).

Molecular Analysis
Molecular genetic studies were performed at Çukurova University AGENTEM (Adana Genetic Diseases Diagnosis and Treatment Center). Informed consent was obtained from patients and their families in accordance with the ethical standards of the institutional ethics committee and the Declaration of Helsinki. DNA isolation from peripheral blood was performed using an automated system (QiаSymphony, Qiagen, Germany) and ready-made kits (DNAmidкit, Qiagen, Germany).

In the preparation of the library, it was first taken to the “fragmentation” stage, and the samples were fragmented. Afterward, the first barcodes were attached to the samples during the “ligation” phase. In the “target polymerase chain reaction (PCR)” stage, target regions for the multigene panel designed in the center were amplified by the PCR method. In the “universal adapter PCR” step, second barcodes and sequencing adapters were attached to the prepared samples. Afterward, the quality and quantity of the created libraries were measured by qPCR, and a library pool was created in accordance with the measurements. The created library pool was loaded into MiSeq (Illumina, San Diego, CA, USA) next-generation sequencing system and sequenced.

Bioinformatic analyses of sequence data obtained from patients were performed in 3 stages. First of all, the quality controls of the sequencing data were made and the suitability of the data for analysis was determined. Afterward, variant analyses of the obtained data and evaluation of the clinical significance of the detected variants were performed. Each of the detected changes was first evaluated through databases (Human Genome Mutation Database, NCBI dbSNP database, and PubMed). The clinical reporting of the disease etiology and/or variants with prognostic importance determined as a result of the analyses was completed by the relevant specialists (physician specialized in Medical Genetics) in accordance with international standards.

Statistical Analysis
Statistical Package for Social Sciences 23.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages and continuous measurements as mean ± SD and median and interquartile range (IQR) where appropriate. The chi-square test and Fischer’s exact test were used to compare categorical variables. The conformity of the variables to the normal distribution was examined using visual
of variance was used. For non-normally distributed data, the Kruskal–Wallis test was used to compare more than 2 groups. The level of statistical significance for all tests was considered to be .05.

**RESULTS**

**Demographical and Clinical Data**

Fifteen (55.5%) of the patients with BS were male and 2 (33.3%) of the GS patients were male. The median age of diagnosis was 4 months (IQR 8) in patients with BS and 174 months (IQR 54) in patients with GS (P < .001) (Table 1). Nine (33.3%) patients with BS diagnosed in the first month of life had phenotypically antenatal BS, and 3 of these patients had SLC12A1, 1 had BSND, and 2 had CLCNKB mutation. The median follow-up period of all patients was 6 years (IQR 7.5). The presenting symptoms are shown in Table 2.

The molecular diagnosis was confirmed in 63.6% (21/33) of patients. Ten patients with BS had CLCNKB, 3 patients had SLC12A1, 1 patient had BSND, 1 patient had CLCNKA, and 6 patients with GS had SLC12A3 mutations. Genetic results of patients are summarized in Table 3.

Polyhydramnios was reported in 3/3 (100%) of SLC12A1, 3/10 (30%) of CLCNKB, 0/1 of CLCNKA, 0/1 of BSND, 0/6 of SLC12A3 patients, and 7/12 (58.3%) of patients without genetic analysis (P = .035). A total of 7 (25%) patients had a history of prematurity. The lowest birth weight among the patients was 880 g. The median gestational age of BS patients was 38 weeks (IQR 6). All patients with prematurity had phenotypically antenatal BS and 3 of these patients had SLC12A1 and 1 had BSND mutation; genetic analysis of other patients with prematurity was not available. The mean gestational age was significantly lower in antenatal BS patients (29 ± 2.0 weeks).

**Table 1. Demographic Features of Patients**

| Symptom                       | Barter Syndrome | Gitelman Syndrome | P   |
|-------------------------------|-----------------|-------------------|-----|
| Sex (female/male)             | 9/18            | 4/2               | .147 |
| Age, mean ± SD (years)        | 6.87 ± 5.09     | 18.50 ± 4.60      | <.001 |
| Age at diagnosis, median (IQR) (months) | 4 (8)          | 174 (54)          | <.001 |
| Follow-up period, mean ± SD (years) | 6.30 ± 5.11    | 5.33 ± 3.25       | .663 |
| Consanguinity (%)             | 23 (85.2)       | 6 (100)           | .429 |
| Family history (%)            | 10 (37)         | 3 (50)            | .442 |

**Table 2. Presenting Symptoms of Patients at Admission**

| Symptoms                        | n (%)         |
|---------------------------------|---------------|
| Polyuria and polydipsia         | 24 (72.7)     |
| Failure to thrive               | 23 (69.7)     |
| Vomiting                        | 12 (36.4)     |
| Facial dysmorphy                | 12 (36.4)     |
| Nephrocalcinosis                | 9 (27.3)      |
| Muscle weakness                 | 6 (18.2)      |
| Hearing loss                     | 2 (6.1)       |

(histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). For comparison of continuous variables between 2 groups, the Student’s t-test or the Mann–Whitney U-test was used where appropriate. For comparison of paired variables measured at diagnosis and at the last visit, the paired t-test was used. For comparison of continuous variables between more than 2 groups, analysis

**Table 3. Genetic Mutations in Patients**

| Patient | Sex | Gene | Nucleotide | Protein | Status      |
|---------|-----|------|------------|---------|-------------|
| 1       | Female | BSND | c.22C>T    | p.R8W   | Homozygous  |
| 2       | Female | SLC12A1 | c.1631C>A | p.S644H | Homozygous  |
| 3       | Female | CLCNKA | c.1159C>T | p.L387F | Heterozygous|
| 4       | Female | SLC12A1 | c.2572C>T | p.R858* | Homozygous  |
| 5       | Male   | CLCNKB | Gene deletion | –     | Homozygous  |
| 6       | Male   | CLCNKB | c.845_847delTCT | p.283delF | Homozygous  |
| 7       | Male   | CLCNKB | Gene deletion | –     | Homozygous  |
| 8       | Male   | CLCNKB | Exon 2-20 deletion | –     | Homozygous  |
| 9       | Male   | SLC12A1 | c.1631C>A | p.S644H | Homozygous  |
| 10      | Male   | CLCNKB | Exon 2-20 deletion | –     | Homozygous  |
| 11      | Female | CLCNKB | Exon 2-20 deletion | –     | Homozygous  |
| 12      | Male   | CLCNKB | c.499-1dupG | IVS5-1dupG | Homozygous  |
| 13      | Male   | CLCNKB | c.228C>T   | p.R76*  | Homozygous  |
| 14      | Male   | CLCNKB | Exon 2-20 deletion | –     | Homozygous  |
| 15      | Male   | CLCNKB | Exon 2-20 deletion | –     | Homozygous  |
| 16      | Female | SLC12A3 | c.602-16G>A | IVS-16G>A | Homozygous  |
| 17      | Female | SLC12A3 | c.1049C>T  | p.S350L | Homozygous  |
| 18      | Male   | SLC12A3 | c.602-16G>A | IVS-16G>A | Homozygous  |
| 19      | Female | SLC12A3 | c.602-16G>A | IVS-16G>A | Homozygous  |
| 20      | Male   | SLC12A3 | c.1387G>A  | p.G463R | Homozygous  |
| 21      | Female | SLC12A3 | c.2576T>C   | p.L859P | Homozygous  |
Table 4. Clinical and Biochemical Characteristics at Presentation of Patients with Confirmed Genetic Mutation

| Parameters                          | Bartter Syndrome | Gitelman Syndrome | P value |
|-------------------------------------|------------------|-------------------|---------|
|                                    | SLC12A1 (n = 3)  | BSND (n = 1)      | CLCNKA (n = 1) | CLCNKB (n = 10) | SLC12A3 (n = 6) |
| Sex (female/male)                   | 2/1              | 1/0               | 1/0       | 1/9            | 4/2            |
| Age at diagnosis, median (IQR) (months) | 2.5              | 0.5               | 4         | 6 (73.3)       | 174 (54)       |
| Gestational age, mean ± SD (weeks)  | 28 ± 0.0         | 32                | 38        | 38.20 ± 0.63   | 38.0 ± 0       |
| Height SDS, mean ± SD               | −3.56 ± 1.74     | −4.0              | −0.19     | −1.87 ± 2.12   | −1.32 ± 0.83   |
| Weight SDS, mean ± SD               | −4.7 ± 1.82      | −4.2              | −1.2      | −2.54 ± 1.99   | −1.77 ± 1.05   |
| Birth weight, mean ± SD (g)         | 1560 ± 597       | 1760              | 3700      | 3270 ± 521     | 2983 ± 349     |
| Sodium, mean ± SD (mmol/L)          | 135.3 ± 6.1      | 125               | 121       | 132.4 ± 8      | 136.8 ± 4.6    |
| Potassium, mean ± SD (mmol/L)       | 3.0 ± 0.1        | 2.70              | 2.90      | 2.58 ± 0.29    | 2.71 ± 0.47    |
| Chloride, mean ± SD (mmol/L)        | 95.0 ± 4.58      | 92.0              | 67.0      | 84.10 ± 11.26  | 97.20 ± 1.30   |
| Bicarbonate, mean ± SD (mmol/L)     | 29.0 ± 4.35      | 44.0              | 48.0      | 36 ± 8.08      | 29.15 ± 1.48   |
| Calcium, mean ± SD (mg/dL)          | 10.40 ± 0.65     | 10.70             | 11.4      | 10.31 ± 0.2    | 9.85 ± 0.57    |
| Magnesium, mean ± SD (mg/dL)        | 2.49 ± 0.17      | 2.30              | 2.30      | 1.63 ± 0.40    | 1.31 ± 0.18    |
| Venous blood pH, mean ± SD          | 7.51 ± 0.06      | 7.54              | 7.63      | 7.56 ± 0.06    | 7.42 ± 0.04    |
| Hypercalcemia, n (%)                | 1 (33.3)         | 0                 | 0         | 1 (100)        | 0              |
| Nephrocalcinosis, n (%)             | 2 (66.6)         | 1 (100)           | 0         | 2 (20)         | 1 (16.6)       |
| Hypomagnesemia, n (%)               | 0                | 0                 | 0         | 5 (50)         | 6 (100)        |

± SDS, SD score. *P* values between genetic mutation groups. †Chi-square test. ‡Kruskal–Wallis test. §Analysis of variance.

compared with classical BS (38.20 ± 0.63 weeks) and GS patients (38.0 ± 0 weeks) (P < .001). The consanguineous marriage frequency was found to be 85.2% (23/27) and 100% in BS and GS, respectively (P = .429). The clinical and biochemical characteristics of patients at presentation according to their genotype are shown in Table 4.

Increased renal parenchymal echogenicity was found in 18 (66.6%) BS patients and nephrocalcinosis was found in 9 (33.3%) BS patients. Two (33.3%) patients with GS had increased renal parenchymal echogenicity. Hypercalcemia was found in 6 (22.2%) patients with BS, and nephrocalcinosis was found in only 2 (7.4%) of them.

**Growth Parameters**

The mean height SDS of patients with BS was −2.6 ± 1.94 and −1.73 ± 2.27 at diagnosis and at last visit, respectively (P = .036). However, the mean height SDS of patients with GS was −1.32 ± 0.83 and −1.21 ± 0.55 at diagnosis and at last visit, respectively (P = .696). The boxplot of height SDS of patients is shown in Figure 1.

**Treatment**

Oral potassium supplementation was prescribed for 96.3% (26/27) of patients with BS and 83.3% (5/6) of patients with GS. Oral sodium supplementation was prescribed for 81.5% (22/27) of patients with BS and 16.7% (1/6) of patients with GS. Oral magnesium supplementation was prescribed for 29.6% (8/27) of patients with BS and all patients with GS. Indomethacin was prescribed for 70.4% (19/27) of patients with BS and none of patients with GS. Blood potassium and magnesium levels of patients are shown in Figure 2.

**Prognosis**

Chronic kidney disease stage 2 was found in 5 (18.5%) of patients with BS and CKD stage 3 was found in 4 (14.8%) of patients with BS at the time of diagnosis. At the last follow-up, a total of 12 BS patients had CKD with a mean of 7.79 ± 4.73 years of age; 5 (18.5%) of these patients had CKD stage 2, 5 (18.5%) had CKD stage 3, and 2 (7.4%) had CKD stage 5. Of the 5 patients with BS with CKD stage 2, two had CLCNKB and one had SLC12A1 gene mutation. Also, CLCNKB mutation was detected in 2 of 5 patients with BS with CKD stage 3. Finally, two patients with BS with CKD stage 5 had BSND mutation in one and CLCNKB mutation in the other. There was no statistically significant association of CKD stage with genetic mutation, nephrocalcinosis, prematurity, and hypokalemia. Estimated glomerular filtration rates of all patients with GS were normal at the time of diagnosis and at the last follow-up. Figure 3

![Figure 1](image-url)
shows the plot of the eGFR versus age at the last visit. The mean eGFR values were found to be statistically significantly lower in patients with antenatal BS (75.36 ± 40.13 mL/min/1.73m²) than in patients with classic BS (119.7 ± 61.74 mL/min/1.73m²) and in GS patients (132.33 ± 26.27 mL/min/1.73m²) at the last visit (P = .046).

DISCUSSION

Bartter and Gitelman syndromes are salt-losing tubulopathies characterized by hypokalemic metabolic alkalosis with autosomal recessive inheritance.9 This study describes the clinical course and genotypes of 33 children with BS and GS.

Bartter syndrome type 1, BS type 2, BS type 4a, and BS type 4b usually present with severe findings in the neonatal period; BS type 3 presents with mild symptoms in early childhood. The symptoms of GS occur in late childhood and adulthood, and GS is usually diagnosed at a later age than BS.10 In a study, it was reported that 27 of 35 BS patients were diagnosed before 1 year of age, while only 1 of 10 patients with GS was diagnosed before 1 year of age.11 In accordance with this, the median age of diagnosis was 4 months in patients with BS and 174 months in patients with GS in our study. Topaloglu et al12 reported that BS was found in 49 (21.7%) and GS in 6 (2.6%) out of 226 children with hereditary tubular disorders due to different causes in Turkey. Also, they reported that a history of consanguinity was found in 61.4% of patients with BS and 83% of patients with GS.11 Similarly, in our study, the frequency of consanguineous marriage was found to be very high in BS and GS as 85.2% and 100%, respectively. This situation explains that the incidence of rare diseases in our country is high because consanguineous marriages are very common compared to other populations.

In a cohort of 85 patients with salt-losing tubulopathy, the genotype distribution showed 20 patients (23.5%) with KCNJ1, 20 patients (23.5%) with CLCNKB, 12 patients (14.1%) with SLC12A1, 13 patients (15.3%) with SLC12A3 gene mutations, and 20 patients (23.5%) with no mutation in these 4 genes.13 In another study, it was reported that 17 (37.8%) of patients had CLCNKB, 8 patients (17.8%) had SLC12A1, 8 patients (17.8%) had KCNJ1, 2 (4.4%) of patients had BSND, and 10 (22.2%) of patients had SLC12A3 gene mutations.11 Ten patients (37%) with BS had CLCNKB, 3 patients (11.1%) had SLC12A1, 1 patient (3.7%) had BSND, 1 patient (3.7%) had CLCNKA, and 6 patients (100%) with GS had SLC12A3 gene mutations in our study. Similar to those

![Figure 2. Blood potassium and magnesium levels at diagnosis (left panels) and at last visit (right panels). P-values are based on Student’s t-test.](image-url)
reported from different countries, CLCNKB was the most frequently detected gene in BS patients in our study. Contrary to other studies, there was no KCNJ1 mutation among those who underwent genetic analysis in our study.

Brochard et al reported that all patients with KCNJ1, SLC12A1, and BSND mutations had polyhydramnios and prematurity. Walsh et al reported that polyhydramnios and prematurity were seen in children with SLC12A1 and KCNJ1 mutations. Lee et al reported that polyhydramnios was present in 7 (87.5%) patients with antenatal BS, but none of the patients with classic BS had a history of polyhydramnios. Among the 8 patients with antenatal BS, 4 (50%) patients were born prematurely. In our study, 7 (25%) of 27 patients with BS had a history of prematurity and none of the patients with GS had prematurity. Thirteen (48.1%) patients had a history of polyhydramnios.

Growth retardation is a common manifestation in patients with BS. History of prematurity, electrolyte imbalance, and recurrent episodes of dehydration are the causes of growth retardation. In addition, these patients may be complicated with growth hormone deficiency. Walsh et al reported that the median height SDS at presentation was –1.6, which was not statistically different from the follow-up (–1.2). Also, subgroup analysis of the genotypes revealed no statistical difference between height at presentation and follow-up. Han et al reported that growth retardation was found in 38 (90.5%) of 42 patients with BS type 3. In our study, the mean height SDS of patients with BS was slightly improved with treatment from the diagnosis (–2.6 ± 1.94) and to the last visit (–1.73 ± 2.27). This shows the importance of strict control of electrolyte abnormalities in tubulopathies. Since the diagnosis was made at a later age in children with GS, the height was not affected from the disorder like in patients with BS so that the mean height SDS of patients with GS was not different at diagnosis and at the last visit in our study.

Nephrocalcinosis is seen in BS type 1, BS type 2, and BS type 4 due to hypercalciuria. Brochard et al reported that patients with KCNJ1 and SLC12A1 mutations had nephrocalcinosis, whereas patients with BSND and CLCNKB mutations did not have nephrocalcinosis. In our study, renal echogenicity increased in 18/27 (66.6%) patients with BS, and nephrocalcinosis was found in 9/27 (33.3%) patients. Nephrocalcinosis was present in 2/10 (20%) of patients with CLCNKB mutation and in 3/3 (100%) of patients with SLC12A1 mutation. Also, 1 patient with BSND mutation had nephrocalcinosis.

Chronic kidney disease was seen in patients with BS due to nephrocalcinosis, recurrent episodes of dehydration, long-term treatment with nonsteroidal anti-inflammatory drugs, and chronic hypokalemia. In general, prognosis of GS is good; however, CKD might develop in patients with GS due to chronic hypokalemia or volume depletion and increased renin–angiotensin–aldosterone, which may contribute to renal damage. In a study, CKD was seen in 3 (7.1%) patients with KCNJ1, CLCNKB, and BSND mutations. Lee et al reported CKD stage 3 and more advanced CKD in 2 (7.7%) of 26 patients. Walsh et al reported that 22 (62.9%) of 35 children with BS and 5 (50%) of 10 children with GS had an eGFR < 90 mL/min/1.73 m², and they did not find a significant association of the development of CKD with hypokalemia, nephrocalcinosis, or urinary concentrating ability in their cohort. Similarly, 12 (44.4%) of 27 children with BS had an eGFR < 90 mL/min/1.73 m² in our study, and there was no statistically significant association of CKD stage with genetic mutation, nephrocalcinosis, prematurity,
and hypokalemia. In a cohort from Turkey, it was reported that of 49 patients with Bartter syndrome, 3 (6%) had renal failure (GFR < 25 mL/min/1.73 m²). In our study, CKD stage 2 and more advanced stage CKD was detected in 44.4% (12/27) of the patients with BS, but it was not detected in any of the patients with GS. The reason for the differences in the rate of CKD development in reported studies can be attributed to the number of patients in the studies, the difference in the GFRs threshold value, and the follow-up periods.

The major limitations of our study are the retrospective design and the lack of molecular analysis for all of our patients. In spite of that, we present data from a relatively large number of children with BS and GS from a single center.

CONCLUSION

The patients with BS and GS may have a different clinical course due to the underlying genetic mutation. Genetic analysis is important as it will provide genetic counseling to family and information about the prognosis. In patients with BS, improvement in growth is observed with appropriate treatment and regular follow-up. Since BS and GS require lifelong treatment, treatment compliance and regular close follow-up are important to prevent advanced-stage CKD.

Ethics Committee Approval: This study was approved by Ethics committee of Çukurova University. (Approval No: 92/5, Date: 04/10/2019).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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