Clinical and diagnostic features of Bartter and Gitelman syndromes

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Abstract

Background: Bartter and Gitelman syndromes are autosomal recessive disorders of renal tubular salt handling. Due to their rarity, limited long-term data are available to inform prognosis and management.

Methods: Long-term longitudinal data were analysed for 45 children with pathogenic variants in SLC12A1 (n = 8), KCNJ1 (n = 8), CLCNKB (n = 17), BSND (n = 2) and SLC12A3 (n = 10) seen at a single centre between 1984 and 2014. Median follow-up was 8.9 [interquartile range (IQR) 0.7–18.1] years.

Results: Polyhydramnios and prematurity were seen in children with SLC12A1 and KCNJ1 mutations. Patients with CLCNKB mutations had the lowest serum potassium and serum magnesium and the highest serum bicarbonate levels. Fractional excretion of chloride was >0.5% in all patients prior to supplementation. Nephrocalcinosis at presentation was present in the majority of patients with SLC12A1 and KCNJ1 mutations, while it was only present in one patient with CLCNKB and not in SLC12A3 or BSND mutations. Growth was impaired, but within the normal range (median height standard deviation score [HSDS] 0.7–18.1] years.

Conclusions: Patients with Bartter and Gitelman syndromes had a satisfactory prognosis during childhood. However, decreased eGFR and pathologic proteinuria was evident in a large number of these patients, highlighting the need to monitor glomerular as well as tubular function. Electrolyte abnormalities were most severe in CLCNKB mutations both at presentation and during follow-up. Fractional excretion of chloride prior to supplementation is a useful screening investigation in children with hypokalaemic alkalosis to establish renal salt wasting.

Key words: Bartter syndrome, chronic kidney disease, Gitelman syndrome, hypokalaemic metabolic alkalosis, renal tubular disease

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Introduction

Bartter syndrome (BS) and Gitelman syndrome (GS) are rare autosomal recessive tubulopathies with a prevalence of ~1 in 100,000 and 25 in 100,000, respectively [1]. BS occurs as a result of mutations in genes coding for proteins mainly responsible for salt and water reabsorption in the thick ascending loop of Henle (TAL), while dysfunction of the sodium chloride co-transporter in the distal convoluted tubule (DCT) results in GS. BS can be further subdivided based on the underlying genetics (Table 1) [2–6].

Two broad phenotypes exist in BS: antenatal BS, due to mutations in SLC12A1, KCNJ1, BSND (with sensorineural hearing loss) and in some cases of CLCNKB; and classic BS, typically associated with mutations in CLCNKB. Recently a transient antenatal BS was described in boys with mutations in MAGED2 [7]. Biochemical hallmarks of BS and GS include hyperaldosteronism with hypokalaemia, hypochloraeic metabolic alkalosis.

Some specific biochemical abnormalities can give clues as to the underlying genotype, summarized in Table 1. For example, patients with KCNJ1 mutations can present with transient hyperkalaemia followed by the more typical hypokalaemia; increased urinary calcium excretion and nephrocalcinosis are present in SLC12A1 and KCNJ1 mutations, whereas patients with SLC12A3 mutations have hypocalciuria, and patients with CLCNKB and SLC12A3 mutations typically develop hypomagnesaemia.

As with most rare diseases, there is little data available about the long-term disease course to inform management and prognosis. In this study we describe the presenting features and long-term outcomes of 45 patients with BS and GS.

Materials and methods

Demographic data

Biochemical and clinical data were analysed for 45 children presenting to Great Ormond Street Hospital (GOSH) between 1984 and 2014. Results were collected at presentation and throughout follow-up, summarized in Table 2. Estimated glomerular filtration rate (eGFR) was calculated using the modified Schwartz formula, with a k-value of 33 [8]. The median follow-up was 8.9 [interquartile range (IQR) 0.5–18.1] years.

Statistical analysis

Data analysis was performed using SPSS (IBM, Armonk, NY, USA). Patients were analysed according to the underlying disease—SLC12A1, KCNJ1, CNCKB, BSND and SLC12A3—to investigate genotype/phenotype correlation. The Mann–Whitney U test was used to investigate differences between individual genotypes and Kruskal–Wallis was used to evaluate differences between multiple groups; statistical significance was defined as P < 0.05.

Median values are given with IQRs throughout. Due to the small size, the BSND group was excluded from statistical analysis.

Molecular analysis

Genotyping was performed by the North East Thames Regional Genetics Service, located at GOSH, using a kit to assess a panel of 37 tubular disease genes, as described previously [9].

Results

Molecular results

Mutations in disease-causing genes are summarized in Table 3. Homozygous variants were identified in 30/45 patients and compound heterozygous variants in the remaining 15/45 patients. Whole gene deletion was responsible for 50% of mutations in CLCNKB.

Initial presentation

Biochemical and clinical features at presentation are summarized in Table 2 and Figure 1.

Prenatal and perinatal history

Polyhydramnios was documented in 8/8 of SLC12A1, 7/8 KCNJ1, 7/17 CLCNKB, 1/2 BSND and 0/10 SLC12A3 cases. Gestational age (GA) was significantly lower in SLC12A1, KCNJ1 and BSND mutations compared with CLCNKB and SLC12A3 (P < 0.001).

Diagnosis and presentation

The diagnosis of BS or GS was made before the age of 1 year in 27/35 BS patients (8/8 SLC12A1, 8/8 KCNJ1, 9/17 CLCNKB and 2/2 BSND) compared with 1/10 GS patients. Children diagnosed before 1 year of age presented with a history of polyhydramnios, polyuria and hypochloraeic metabolic alkalosis. The remaining patients were diagnosed during childhood with failure to thrive (four CLCNKB), persistent muscle cramping (one CLCNKB, one SLC12A3), fainting spells (one SLC12A3) and incidentally noted biochemical derangement during intercurrent illness (one CLCNKB, seven SLC12A3).

Median plasma potassium concentration at presentation was lowest in CLCNKB mutations [2.6 mmol/L (IQR 2.1–2.9)],

Table 1. Clinical and genetic classification of BS and GS

| Clinical phenotype | OMIM       | Genetic subtype | Gene/locus | Protein | Features                      |
|-------------------|------------|----------------|------------|---------|-------------------------------|
| Antenatal BS      | 601678     | Type I         | SLC12A1/15q21.1 | NKCC2   | Polyhydramnios, prematurity, polyuria, nephrocalcinosis, failure to thrive |
| Antenatal BS      | 241200     | Type II        | KCNJ1/11q24.3 | ROMK1   | Polyhydramnios, prematurity, polyuria, nephrocalcinosis, failure to thrive |
| Classic BS        | 607364     | Type III       | CLCNKB/1p36.13 | CLC-Kb  | Failure to thrive, hypomagnesaemia |
|Antenatal BS with sensorineural deafness | 602522 | Type IV | BSND/1p32.3 | Barttin | Polyhydramnios, prematurity, polyuria, nephrocalcinosis, failure to thrive, sensorineural deafness |
| GS                | 263800     | GS             | SLC12A3/16q13 | NCCT    | Hypocalciuria, hypomagnesaemia |
| Transient antenatal BS | 300971 | Type V         | MAGED2       | MAGED2  | Severe polyhydramnios, prematurity, hypercalciuria, spontaneous resolution |

OMIM: Online Mendelian Inheritance in Man.
while two children with KCNJ1 were noted to have transient hyperkalaemia at presentation (Figure 1).

Fractional excretions of chloride (FECl) and sodium (FENa) at presentation were calculated in children where the data were available (FECl in 15 children and FENa in 28 patients) and are summarized in Table 2. FENa ranged from 0.1 to 6.4%, while FECl >0.5% was seen in all patients with available data, prior to commencing supplementation. In patients where both values were available (n = 15), the median FENa was 0.7% (IQR 0.3–1.2) and FECl was 1.62% (IQR 1.2–5.5).

Normal urine calcium:creatinine (UCC) ratio varies with age, therefore the results were normalized to an age-adjusted upper limit of normal. This was elevated in 5/8 SLC12A1, 5/8 KCNJ1, 7/17 CLCNKB and 2/2 BSND patients. Ultrasound scan at presentation was performed in all children as a screen for nephrocalcinosis; this was seen in 8/8 SLC12A1, 8/8 KCNJ1, 2/17 CLCNKB, 0/2 BSND and 0/10 SLC12A3 patients.

**Table 2. Clinical and biochemical characteristics at presentation**

| Parameter                      | BS (n = 8)          | KCNJ1 (n = 8)        | CLCNKB (n = 17)     | BSND (n = 2)       | SLC12A3 (n = 10) | P-value |
|--------------------------------|---------------------|----------------------|---------------------|-------------------|-----------------|---------|
| GA, weeks                      | 32 (27–33)          | 30 (28–33)           | 40 (38–40)          | 32                | 40 (40–40)      | <0.001  |
| Polyhydramnios, present/absent| 8/0                 | 7/1                  | 7/10                | 0/2               | 0/10            | <0.001  |
| Sex, M/F                       | 4/4                 | 4/4                  | 12/5                | 0/2               | 7/4             | N.S.    |
| Height, Z-score                | –1.28 (–4.9 to –0.62) | –2.2 (–3.0 to 0.4) | –2.1 (–4.9 to –0.11) | 0/2               | 7/4             | N.S.    |
| Weight, Z-score                | –3.49 (–4.22 to 1.00) | –2.31 (–3.49 to –0.22) | –1.82 (–3.49 to –0.63) | 0/2               | 7/4             | N.S.    |
| Sodium, [133–146 mmol/L]       | 146 (143–148)       | 142 (135–148)        | 135 (130–140)       | (116–130)         | 139 (135–140)   | 0.001   |
| Potassium [3.5–5.5 mmol/L]     | 3.4 (2.9–3.9)       | 3.8 (3.6–6.0)        | 2.6 (2.1–2.9)       | (2.1–3.0)         | 2.8 (2.4–3.0)   | <0.001  |
| Chloride [96–106 mmol/L]       | 103 (98–110)        | 103 (101–109)        | 95 (81–98)          | (59–79)           | 98 (96–101)     | 0.001   |
| Bicarbonate [18–28 mmol/L]     | 25 (25–29)          | 25 (23–28)           | 29 (26–33)          | (24–81)           | 30 (28–31)      | 0.01    |
| Magnesium [0.6–0.9 mmol/L]     | 0.97 (0.91–1.17)    | 0.94 (0.73–1.07)     | 0.76 (0.59–0.90)    | (0.55–0.74)       | 0.67 (0.58–0.83) | 0.005   |
| FENa, %                        | 0.36 (0.17–1.23)    | 0.82 (0.37–2.51)     | 0.87 (0.39–1.25)    | Not obtained      | 0.55 (0.30–0.95) | N.S.    |
| FECl, %                        | 1.6 (0.8–5.4)       | 1.25 (N/A)           | 3.9 (1.4–6.1)       | Not obtained      | 2.1 (N/A)       | N.S.    |
| Age-adjusted calcium:creatinine ratio, normalized to upper limit of normal | 1.17 (0.88–2.00) | 1.37 (0.82–2.04) | 0.61 (0.14–1.34) | (1.50–1.64) | 0.09 (0.05–0.21) | <0.001 |
| Nephrocalcinosis, present/absent| 8/0                 | 8/0                  | 2/15                | 0/2               | 0/10            | <0.001  |

Median values given with interquartile ranges in parentheses. Reference range given in square brackets. Superscript numbers indicate the number of patients with missing data. P-values for Kruskal–Wallis analysis comparing SLC12A1, KCNJ1, CLCNKB and SLC12A3: M: male; F: female; N.S.: Not significant.

**Course of clinical and biochemical data**

**Growth**

The median height [standard deviation score (SDS)] at presentation was –1.6 (IQR: –3.88 to –0.04), this was not statistically different from the follow-up [-1.2 (IQR: –3 to –1.7)]. Subgroup analysis of the genotypes revealed no statistical difference between height at presentation and follow-up (SDS): SLC12A1, P = 0.35; KCNJ1, P = 0.6; CLCNKB, P = 0.39; SLC12A3, P = 0.59.

**Growth hormone treatment**

Growth hormone (GH) deficiency has previously been reported in children with BS [11]. In this cohort, GH was used in three patients (1, 10 and 23) due to documented GH deficiency based on formal glucagon stimulation tests. In Patient 1, it was started at the age of 8 years, when her height was 110 cm (SDS –3.29). She was also treated with gonadotropin-releasing hormone analogues to delay puberty. Treatment was stopped at the age of 16 years, when her height was 153 cm (SDS –1.42). Patient 10 started GH at the age of 14 years, when his height was 126 cm (SDS –4.37) and was stopped at the age of 17 years, when his height was 154 cm (SDS –3.02).

Patient 23 started GH at the age of 6 years when his height was 102 cm (SDS –3.78). This coincided with indomethacin being discontinued due to a gastrointestinal bleed. His height SDS remained essentially unchanged for the following 2 years (SDS –3.88) despite GH treatment. At the age of 8 years, indomethacin was restarted (and GH continued) and his height SDS improved to –2.75 over the following year. At the last follow-up (still on GH and indomethacin) at the age of 12 years, his height was 133 cm (SDS –2.26).

**Persistent hypokalaemia**

Persistent hypokalaemia, defined as potassium <3.5 mmol/L on at least two consecutive blood tests, was seen in 41 children. Mild hypokalaemia (2.5–3.5 mmol/L) was present in 28 children (BS 26, GS 6), moderate hypokalaemia (2.0–2.5 mmol/L) was seen in 9 children (BS 6, GS 3) and severe hypokalaemia (<2.0 mmol/ L) was noted in 4 children (3 CLCNKB and 1 BSND).

At the last follow-up, plasma potassium was decreased (<3.5 mmol/L) in 36 patients (BS 26/35 and GS 10/10). Plasma bicarbonate was elevated (>28 mmol/L) in 20 patients (BS 18/35 and GS 2/10) and plasma magnesium was decreased (<0.6 mmol/L) in 7 patients (BS 3/35 and GS 4/10) (Figure 1).

**Complications**

Two children with CLCNKB mutations were admitted for optimization of potassium supplementation (serum potassium 1.3 mmol/L and 1 mmol/L), one due to symptoms of hypokalaemic paralysis (Patient 13), which resolved following increased potassium supplementation, and the second due to concerns regarding compliance (Patient 15).

The median serum magnesium level at the last follow-up was lowest in GS patients [0.62 mmol/L (IQR 0.55–0.71)]. Hypomagnesaemia was associated with both CLCNKB and SLC12A3 mutations; while there was a trend to lower magnesium with increasing age, this was not statistically significant. No arrhythmias were noted.
Table 3. Causative mutations identified

| Gene    | Patient | Sex | Nucleotide | Protein                  | Status                  |
|---------|---------|-----|------------|--------------------------|-------------------------|
| SLC12A1 | 1       | Female | c.1316G>A  | p.(Arg439Gln)            | Homozygous              |
|         | 2       | Male   | c.1215G>A  | p.? (loss of splice site) | Homozygous              |
|         | 3       | Female | c.811G>C/c.116C>G | p.(Asp271Pro/p.Arg439Gln) | Compound heterozygous   |
|         | 4.1     | Female | c.450_451del/c.967G>A | p.(Asp150Glufs*4)/p.(Glu323Lys) | Compound heterozygous |
|         | 4.2     | Male   | c.450_451del/c.967G>A | p.(Asp150Glufs*4)/p.(Glu323Lys) | Compound heterozygous |
|         | 5       | Male   | c.1327G>A/c.2805dup | p.(G443R)/p.(Trp936fs) | Compound heterozygous   |
|         | 6.1     | Male   | c.3165_?-1_?del | p.? (exon 26 deletion) | Homozygous              |
|         | 6.2     | Female | c.3165_?-1_?del | p.? (exon 26 deletion) | Homozygous              |
| BSN1    | 7       | Male   | c.1-1_?del | p.? (exon 1 deletion)    | Homozygous              |
|         | 8       | Male   | c.277T>G   | p.(Phe93Val)             | Homozygous              |
|         | 9.1     | Female | c.716delG  | p.(Gly239Glufs*14)       | Homozygous              |
|         | 9.2     | Female | c.658C>T   | p.(Leu220Pro)            | Homozygous              |
|         | 10      | Female | c.657C>G   | p.(Ser219Arg)            | Homozygous              |
|         | 11      | Male   | c.657C>G   | p.(Ser219Arg)            | Homozygous              |
|         | 12      | Male   | c.657C>G   | p.(Ser219Arg)            | Homozygous              |
| CLCNK2  | 13      | Male   | c.?_?-1_?del | p.? (gene deletion)     | Homozygous              |
|         | 14.1    | Female | c.875G>T   | p.(Cys292Pro)            | Homozygous              |
|         | 14.2    | Female | c.875G>T   | p.(Cys292Pro)            | Homozygous              |
|         | 15      | Female | c.?_?-1_?del | p.? (gene deletion)     | Homozygous              |
|         | 16      | Female | c.?_?-1_?del | p.? (gene deletion)     | Homozygous              |
|         | 17      | Male   | c.1093del c.968+1G>A | p.(Glu565Argfs*7)/p.(?) | Compound heterozygous   |
|         | 18      | Male   | c.?_?-1_?del | p.? (gene deletion)     | Homozygous              |
|         | 19      | Male   | c.?_?-1_?del | p.? (gene deletion)     | Homozygous              |
|         | 20      | Female | c.1987A>T  | p.(Arg663)               | Homozygous              |
|         | 21      | Male   | c.1395delG | p.(Tyr465?)              | Homozygous              |
|         | 22      | Male   | c.?_?-1_?del | p.? (gene deletion)     | Homozygous              |
|         | 23      | Male   | c.?_?-1_?del | p.? (gene deletion)     | Homozygous              |
|         | 24      | Male   | c.?_?-1_?del | p.? (gene deletion)     | Homozygous              |
|         | 25      | Male   | c.182C>A/c.373G>A | p.(Asp61Asp/p.(Gly125Lys) | Compound heterozygous |
|         | 26      | Male   | c.1897delC | p.(Leu633)              | Homozygous              |
|         | 27      | Female | c.1929+1G>A/c.887G>A | p.?/p.(Gly296Asp) | Compound heterozygous |
|         | 28      | Male   | c.182C>A/c.373G>A | p.(Asp61Asp/p.(Gly125Lys) | Compound heterozygous |
| BSN1    | 29      | Female | c.452delC | p.(Pro151Leufs*27)      | Homozygous              |
| SLC12A3 | 30      | Female | c.125G>A/c.139G>A | p.(Ser42Asn)/p.(Gly47Arg) | Compound heterozygous   |
|         | 31      | Male   | c.2221G>A/c.3002G>A | p.(Gly741Arg/p.(Ala1001Asp) | Compound heterozygous |
|         | 32      | Male   | c.1202C>A/c.2965 | p.(Asp61Asp/p.(Gly989Arg) | Compound heterozygous   |
|         | 33      | Male   | c.2221G>A/c.3052C>T | p.(Gly741Arg/p.(Arg1018*) | Compound heterozygous |
|         | 34      | Female | c.2878_2879insAGGGTTGACCCCTG | p.(Val960Glufs*12) | Homozygous              |
|         | 35.1    | Female | c.626G>A/c.1577A>G | p.(Arg209Gln/p.(Asp526Ser) | Homozygous              |
|         | 35.2    | Female | c.626G>A/c.1577A>G | p.(Arg209Gln/p.(Asp526Ser) | Homozygous              |
|         | 36      | Male   | c.647G>A/c.2221G>A | p.(Gly216Glu/p.(Gly741Arg) | Compound heterozygous   |
|         | 37      | Male   | c.424G>T/c.2952_?-1_?del | p.(Val142Leu/p.(?)Exon 26 deletion) | Compound heterozygous |
|         | 38      | Female | c.2221G>A | p.(Gly741Arg)            | Compound heterozygous   |
|         | 39      | Male   | c.506_1G>A/c.1180_+1G>T | p.? (splice site) | Compound heterozygous |

Medications at last follow-up

Sodium supplementation was prescribed for 14/45 patients (BS 12/35 and GS 2/10), potassium supplementation for 38/45 patients (BS 30/35, GS 8/10) and magnesium supplementation for 12/45 patients (BS 7/35 and GS 5/10). Prostaglandin inhibitors (ibuprofen or indomethacin) were prescribed in 20/45 patients (BS 20/35 and GS 0/10).

Side effects of medication

Indomethacin

Indomethacin was used in 30/35 BS and 2/10 GS patients. Indomethacin was permanently discontinued in three children: two developed abdominal pain (Patients 17 and 24) and one developed excessive bruising days after commencing treatment (Patient 23).

Indomethacin was temporarily discontinued in two other children. One child (Patient 8) developed necrotizing enterocolitis at 17 days of age; indomethacin was eventually recommenced at 3 months due to ongoing severe polyuria. The second child developed gastrointestinal bleeding during the first year of life (Patient 21); indomethacin was gradually reintroduced. Indomethacin was substituted with ibuprofen in four patients: two because of parental preference (Patients 9.1 and 9.2), one due to abdominal pain that settled after switching (Patient 4.1) and one who developed peptic ulcer disease...
that settled with antacid treatment and switching to ibuprofen (Patient 20).

**Potassium-sparing diuretics**

Spironolactone was used in 6/35 BS patients. In one (Patient 24), it was discontinued at age 15 years due to gynaecomastia and in a second (Patient 15) it was discontinued due to lack of biochemical improvement. One patient received amiloride because of dramatic alkalosis (Patient 29) [10].

**Chronic kidney disease**

At the last follow-up, 27/45 children (BS 22/35 and GS 5/10) had an eGFR <90 mL/min/1.73 m². Pathological albuminuria (urine...
albumin:creatinine ratio >2.5 mg/mmol in boys and >3.5 mg/mmol in girls) was detected in 31/45 children (BS 28/35 and GS 3/10). There was no statistically significant association of development of CKD with either hypokalaemia, nephrocalcinosis or urinary concentrating ability.

One child (patient 24) with BS Type 3 developed nephrotic-range proteinuria (3.3 g/day) and underwent a kidney biopsy at the age of 14 years, when his eGFR was 60 mL/min/1.73 m², which demonstrated focal segmental glomerular sclerosis. An angiotensin-converting enzyme inhibitor was commenced at low dose (enalapril 0.06 mg/kg/day), but was temporarily stopped due to an increase in creatinine by almost 50% (from 123 to 183 μmol/L). When subsequently restarted at half the dose, proteinuria decreased to 1.8 g/day with stable plasma creatinine (135 μmol/L).

One patient with CKD Stage 3 (Patient 33) had been diagnosed with vesico-ureteric reflux at 3 years of age after suffering from recurrent urinary tract infections.

Urinary concentrating ability
Maximal urine osmolalities (Uosm) obtained at clinic visits were compared according to genotype for those with available data. The average maximal Uosm in patients with SLC12A1 and KCN1 mutations was 285 ± 8 (SEM) mOsm/kg (n = 11), compared with 547 ± 17 for CLCNKB (n = 12) and 653 ± 65 for SLC12A3.

In all, six patients (all with antenatal BS) had formal desmopressin (DDAVP) tests because of concerns over the urinary concentrating ability. Of these, four patients (1, 2, 8 and 9.1) showed evidence of secondary nephrogenic diabetes insipidus (sNDI) with Uosm below plasma osmolality (Posm) after DDAVP. The two others (Patients 9.2 and 12) showed evidence of isosthenuria, with Uosm only mildly increasing to 345 and 367 mOsm/kg, respectively, after stimulation with DDAVP.

Extrarenal complications
Intellectual impairment was not systematically evaluated in all patients but was documented in three patients (2, 10, 11.1) and was mostly ascribed to complications from prematurity. Patient 10 also has ataxia with cerebellar atrophy, which was deemed familial, as his sister and aunt (who do not have BS) are also affected.

Discussion
This study describes the long-term outcome for a large cohort of patients with BS and GS. Overall, the prognosis appears reasonable, with the most serious complications related to prematurity. Genotype-phenotype correlation broadly confirms results seen in previous cohorts.

Growth
Growth was below average for the cohort, but the mean height was within two standard deviations. Height SDS improved slightly with treatment, from –1.6 at presentation to –1.2 at the last follow-up. GH deficiency has been recurrently reported in BS [11, 12–15]. In our cohort, three patients were treated with GH. Of interest is the observation in Patient 23, with BS Type 3, only showed catch-up growth with concomitant non-steroidal anti-inflammatory drug (NSAID) treatment. Most reports of GH deficiency in BS concern patients with CLCNKB mutations, the type of BS with the most severe biochemical abnormalities. This raises the question whether GH secretion and response is impaired by severe hypokalaemia, alkalosis and/or elevated prostaglandins. Reports of GH deficiency in patients with GS would argue against an effect of prostaglandins [16, 17]. Yet, these reported patients had no genetic confirmation of the diagnosis, thus it is unclear if they truly had GS or rather BS Type 3. More systematic investigations are needed to address this question.

Treatment
Supplementation with sodium and/or potassium was the most frequently prescribed intervention; this is in keeping with previously described cohorts [18–20]. Yet, the small differences in potassium levels between presentation and follow-up (see Figure 1) demonstrate the difficulties in improving this parameter by supplementation, as an increased blood level results in an increased filtered load and thus, typically, increased urinary losses.

In our cohort, treatment with NSAIDs at the last follow-up was used in more than half of children with BS. Treatment with NSAIDs was generally well tolerated, although side effects that prompted temporary or permanent withdrawal were seen in seven patients. Such withdrawal occurred with indomethacin, yet this was also the most frequently used NSAID. Thus, whether complications are more commonly associated with indomethacin compared with other NSAIDs cannot be answered from our study. Treatment with so-called cyclooxygenase-2 inhibitors has been suggested for patients with BS, and we increasingly prescribe it in our current patients, but none of the patients in this historic cohort received this class of drug [21].

Treatment and tolerance of hypokalaemia is a controversial topic in hypokalaemic alkalosis, as hypokalaemia can be associated with complications, yet excessive supplementation can also be harmful [22]. Interestingly, despite persistent hypokalaemia (serum potassium <3.0 mmol/L) in 35/45 patients during follow-up, only 1 patient experienced overt symptoms, in the form of hypokalaemic paralysis (serum potassium 1.3 mmol/L); no arrhythmias were detected with hypokalaemia, but this was also not routinely screened for.

The classic clinical features of hypovolaemia, hyperaldosteronism and the consequent hypokalaemic, hypochloraeic metabolic alkalosis can be seen with both renal and extrarenal salt-wasting states, e.g. chronic and severe gastro-oesophageal reflux or congenital chloride diarrhoea, and it can be challenging to distinguish between them. The data presented in this cohort suggest that FENa cannot reliably distinguish between renal and extrarenal salt wasting. This is consistent with the concept that in the long-term salt homeostasis must be in a steady state, as persistent excess salt excretion would lead to life-threatening hypovolaemia. In this cohort, all patients with available data had an FENa >0.5% prior to commencing electrolyte supplementation, suggesting that this may be a better indicator for renal salt loss, as FENa in extrarenal salt-losing conditions is expected to be minimal. Given the importance of sodium for volume homeostasis, the tubules prioritize sodium reabsorption above other cations, especially potassium, so that sodium losses can be minimized. However, both sodium and potassium need to be accompanied by an anion, typically chloride and therefore FENa is better suited to detect renal salt wasting. Obviously these measurements should be obtained prior to supplementation, or when the patient is clinically hypovolaemic. After commencing supplementation, increased renal excretion may simply reflect the increased intake.
Chronic kidney disease

Impaired GFR and pathological glomerular proteinuria was seen in a substantial number of children during follow-up, in keeping with previous cohorts [19, 20, 23, 24]. In our cohort this was more common in BS than GS. There are a number of possible explanations for this. One possibility is that this is secondary to nephrocalcinosis; however, in the four children with CLCNKB mutations and CKD, there was no evidence of nephrocalcinosis, suggesting this is not the cause in these patients. Long-term treatment with NSAIDs is linked to an increased risk of CKD [25], however, the doses used in BS and GS are relatively small (typically 1–2 mg/kg/day of indomethacin) compared with doses used for analgesia. Moreover, patients with BS have increased levels of prostaglandins involved in the regulation of renal perfusion and treatment with NSAIDs does not suppress these, but brings them closer to the normal range. Previous data suggest that the use of NSAIDs in children with BS is not linked to histological evidence of NSAID-induced renal damage [18].

A third possibility is chronic hypokalaemia, which in rats leads to hypertrophy and ultimately renal fibrosis with elevated transforming growth factor β [26]. Yet, results from adults with BS and GS suggest that the severity of hypokalaemia is not directly linked to the degree of CKD [27].

Stimulants of the renin-angiotensin–aldosterone system in BS and GS include chronic volume depletion, and in BS, ‘short-circuiting’ of the juxta-glomerular apparatus [6, 10]. There is experimental and epidemiological work that demonstrates a damaging effect of elevated aldosterone levels on podocytes, thus leading to CKD [28, 29]. Potentially this may also contribute to the CKD seen in children with BS and GS.

Prematurity is an emerging risk factor for CKD [30]. As human nephrogenesis is not complete until 36 weeks post-gestation, children born prematurely have an incomplete endowment of nephrons and therefore undergo ex utero nephrogenesis. In our cohort, patients with CLCNKB mutations and CKD were born at term, thus prematurity in these children is unlikely to be the primary cause of CKD in these patients, but it is a likely contributor in patients with antenatal BS.

The progression of CKD in BS and GS is likely multifactorial and therefore patients need regular follow-up to monitor glomerular as well as tubular function.

Urinary concentrating ability

We previously reported the presence of an sNDI in two patients (1 and 2) [31, 32] and confirm this complication in two further patients with marked polyuria (8 and 9.1). In contrast, the sister of Patient 9.1 (9.2), as well as Patient 12, showed isothenuria, consistent with dysfunction of the loop of Henle [33]. While sNDI is seen only in patients with antenatal BS, the discrepant findings in the siblings Patients 9.1 and 9.2 argue against a clear genotype effect; we also did not note substantial differences in their plasma electrolytes or urinary calcium concentration. Clinically these patients pose a management problem: BS is primarily a salt-wasting disorder and consequently supplementation with salt is a mainstay of treatment. Yet, patients with NDI need to minimize their salt intake to reduce the osmotic load. Indeed, the patients with confirmed sNDI all had recurrent hypernatraemic dehydration (maximal plasma sodium concentrations of 165, 161, 148 and 153 mmol/L) and salt supplementation was either never prescribed or discontinued in these four patients.

In summary, we report a large cohort of children with BS and GS with long-term follow-up data treated in a single centre over a 30-year period. This demonstrates the overall prognosis in children with BS and GS is reasonable; the majority of children reached a height that was within the normal range and there were very few complications resulting from extreme electrolyte abnormalities. In this cohort, impaired GFR and pathological albuminuria were seen in a large proportion of children, highlighting the need for follow-up of glomerular as well as tubular function in these patients.

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Conflict of interest statement

None declared.

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