Molecular Genetics and Metabolism Reports 40 (2024) 101112

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Clinical, genetic characteristics and outcome of four Chinese patients with Bartter syndrome type 3: Further insight into a genotype-phenotype correlation

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ARTICLE INFO

Keywords:
Bartter syndrome
Hypokalemia
CLCNKB gene
Gene mutation

ABSTRACT

Aim: To investigate the characteristics of 4 Chinese patients with Bartter syndrome type 3 (BS Type 3).
Methods: The clinical data, genetic analysis, and outcome of four cases with Bartter syndrome type 3 were retrospectively summarised.
Results: Gene sequencing analysis showed that all children carried a compound heterozygous mutation in the *CLCNKB* gene and were diagnosed with BS type 3. All types of mutations were detected, including two missense mutations, one nonsense mutation, one small fragment deletion mutation, two large deletion mutations and one splice-site mutation. The splice-site mutation c.100 + 1 (IVS2) C > T was novel. Two cases carried large deletion mutations. The patients presented as classic BS with modest manifestations. The most common sign was growth retardation. There was no polyhydramnios or preterm delivery. All cases were treated with potassium chloride supplementation and indomethacin. During long-term follow-up, clinical symptoms and growth retardation improved significantly. Nephrocalcinosis or renal dysfunction was not observed.
Conclusion: The clinical manifestations of BS type 3 are mostly presented as cBS. Growth retardation is a common sign. BS type 3 had a good long-term prognosis. There were various types of mutations in the *CLCNKB* gene. Large deletions were the most common.

1. Introduction

Bartter syndrome (BS) is a rare hereditary disorder of the renal tubules that was first discovered and named by Bartter in 1962 [1]. BS is characterized by hypokalemic metabolic alkalosis with renin, angiotensin, and aldosterone elevation but normal blood pressure. The incidence of BS is estimated at 1:40,000–50,000 in Western countries [2]. Asia reports the highest number of cases, followed by Europe [3].

Based on molecular genetics, six pathogenic genes including *SLC12A1* gene, *KCNJ1*gene, *CLCNKB* gene, *CLCNKA* gene, *BSND* gene, *MAGED2* gene were identified and accordingly five genetic subtypes (BS type 1–5) were classified [4]. BS type 3 is the most common in China, South Korea, Japan, and Turkey [5–8]. BS type 3 is caused by a loss-of-function mutation in *CLCNKB* gene which is located at 1p36 and comprises 20 exons, first reported by Simon et al. in the United States in 1997 [9]. The gene encodes chloride voltage-gated channel (CLC)-Kb, which consists of 687 amino acids. It is a homodimer, with each subunit consisting of 18 alpha-helical structures (A-R) and two cystathionine-beta-synthase structures at the intracellular C-terminus [10]. CLC-Kb is expressed in the thick ascending limb of the loop of Henle, the distal tubules, and the collecting ducts of the kidney. It plays an essential role in the transport and reabsorption of chloride ions. The *CLCNKB* gene mutations can lead to decreased expression of CLC-Kb on the cell membrane, decreased membrane stability, and reduced channel function [11,12]. Abnormal Cl^- reabsorption in the renal tubules changed the solute gradient of the medullary loop. As a result, Na^+ and water reabsorption were reduced, which activated the renin–angiotensin–aldosterone system. Hyperreninemic hyperaldosteronism led to increasing Na^+ reabsorption and exacerbation of K^+. In addition, long-term elevation of angiotensin II can increase prostaglandin E, which is involved in vasodilation. As a result, the activation of the renin–angiotensin–aldosterone system did not cause

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https://doi.org/10.1016/j.ymgmr.2024.101112
Received 2 April 2024; Received in revised form 23 May 2024; Accepted 22 June 2024

hypertension [13].

Previous studies have shown significant phenotypic variability of BS type 3 [14]. It frequently manifests as classic BS (cBS), also antenatal BS (aBS) or Gitelman-like syndrome [15]. cBS is a typical phenotype that is most observed in infants and young children. It mainly manifests with mild symptoms, such as growth retardation, polydipsia, polyuria, thirst, vomiting, constipation, salt preference, bilateral lower-limb weakness, and malnutrition. aBS is manifested in prenatal onset with polyhydramnios, low birth weight, failure to thrive, hypercalciuria, and hyperprostaglandin E [16]. Gitelman-like syndrome is characterized by hypocalciuria and hypomagnesemia, like the Gitelman syndrome [17].

BS type 3 requires lifelong potassium chloride supplementation. Potassium chloride supplementation is recommended at an initial dose of 2 mmol/kg/day, with a maximum dose of 8 mmol/kg/day [18]. Cyclooxygenase inhibitor should be used, Indomethacin is commonly used, with a recommended dose of 1–4 mg/kg/day divided into 3–4 doses [4,19]. It is recommended to start with a low dose and to closely monitor renal function and gastrointestinal ulcers. Previous studies have suggested that spironolactone can improve hypokalemia and alkalosis. However, BS is a salt-losing disease, and diuretics may worsen the salt wasting and risk critical hypovolemia. In 2021, the consensus of European Rare Kidney Disease Reference Network Working Group for Tubular Disorders explicitly states that routine use of potassium-sparing diuretics is not recommended for treating all types of BS [4].

In this study, we retrospectively summarised the clinical characteristics and long-term follow-up results of four Chinese children with BS type 3. Furthermore, by analysing our data and the data of the previous study, we showed the description of phenotype and genotype of BS type 3 to further understand the phenotypic and genotypic characteristics of BS type 3.

2. Materials and methods

2.1. Clinical data

Patients were diagnosed with BS based on their clinical and biochemical findings in the Endocrinology Department of Beijing Children's Hospital. The clinical data of the participants were retrospectively summarised, including gender, age, clinical manifestations, laboratory test results, treatment methods, and follow-up results.

2.2. Genetic analysis

Informed parental consent was obtained before genetic investigations. Genomic DNA was isolated by standard methods from 5 mL of EDTA-treated peripheral whole blood from the patients and their parents, and whole exome sequencing (WES) was performed. Candidate variants were assessed by polymerase chain reaction (PCR) followed by Sanger sequencing. Multiple ligation-dependent probe amplification (MLPA) was performed to validate the large fragment deletion mutation.

3. Results

3.1. Clinical characteristics and biochemical data

The clinical and biochemical data are shown in Table 1. All cases were early onset in infants. Polyhydramnios, premature birth, or low birth weight were not observed. Complaints included failure to thrive, vomiting and incidental hypokalemia. The most common sign was growth retardation.

Significant hypokalemia (plasma potassium: 2.6–2.88 mmol/L) was present in all patients. Moreover, the patients had significant hypochloremia and mild hyponatremia. One patient had mild hypomagnesemia. None of the patients had hypercalcinuria or hypocalcinuria. None of the participants had nephrocalcinosis or renal dysfunction.

Table 1
Clinical and laboratory data of patients with BS type 3 and long-term prognosis.

	Case 1	Case 2	Case 3	Case 4
Gender	male	male	male	male
Age of onset	3 m	9 m	11 m	0.5 m
Birth weight (kg)	3	3.15	3.1	4.45
Premature	No	No	No	No
Weight (kg)	5.5(−2.1 SD)	7 (−2.2 SD)	9.2 (−1.4 SD)	6.7 (−1.9 SD)
Length (cm)	62 (−0.9 SD)	68 (−1.8 SD)	76 (−2.0 SD)	68 (−0.5 SD)
Main symptoms	Failure to thrive	Hypokalemia	Vomiting	Failure to thrive
Plasma				
K (mmol/L)	2.88	2.6	2.88	2.87
Na (mmol/L)	133.9	130	133.9	127.5
Cl (mmol/L)	91.7	85	91.7	77.6
Mg (mmol/L)	1.02	0.84	1.02	0.6
PH	7.49	7.509	7.49	not mentioned
HCO3 (mmol/L)	31.8	32.8	31.8	32.7
Renin [ng/(ml·h)]	>4.63	>12	4.63	34.31
Angiotensin II (pg/ml)	390.5	>800	390.5	193.22
Aldosterone (pg/ml)	26.15	184	26.15	746.121
Urine				
K [mmol/(kg·d)]	2.4	2.5	2.4	4.8
Cl [mmol/(kg·d)]	4.74	5.7	4.74	–
Na [mmol/(kg·d)]	2.96	3.5	2.96	5.31
Ca [mmol/(kg·d)]	0.16	0.04	0.16	0.13
Ca /Cr (mmol/mmol)	0.06	0.02	0.94	0.84
Nephrocalcinosis	No	No	No	No
Follow-up(years)	15	15	4	2
Age at last follow-up	15y5m	15y10m	5y11 m	2y8m
Weight (kg)	51 (−0.8 SD)	68 (+0.7 SD)	22 (+0.1 SD)	12.5 (−0.9 SD)
Height (cm)	175 (+0.4 SD)	169 (−0.5 SD)	121 (+0.6 SD)	91 (−0.4 SD)
eGFR (mL/min/1.73 m^2)	Normal	Normal	Normal	Normal
Potassium at last visit (mmol/L)	3.5	3.12	3.1	3.2

3.2. Genetic analysis results:Known and novel mutations

All cases carried a compound heterozygous mutation in the *CLCNKB* gene. We identified 7 mutations. The copy number variation results of two patients suggested large deletions, which were confirmed by MLPA as deletions of exons 1–19 and 2–20, respectively. Details of the mutations detected are shown in Table 2. Two missense mutations, one nonsense mutation, one small fragment deletion mutation, and two large fragment deletions have been previously reported. The splice-site mutation c.100 + 1 (IVS2) C > T was novel.

3.3. Treatment and long-term follow-up

All patients were treated with potassium chloride supplementation and oral indomethacin. Case 3 and Case 4 were treated with spironolactone at the time of the initial diagnosis, which was discontinued 1 year later.

After following up for 2–15 years, the clinical symptoms and growth retardation improved significantly. Improvements were seen in last weight SDS and height SDS compared with the patients' initial presentation. Plasma potassium levels increased, fluctuating between 3.1 and 3.5 mmol/L. No nephrocalcinosis or renal dysfunction was observed.

4. Discussion

In this study we analysed the clinical and molecular characteristics of 4 Chinese pediatric patients with BS type 3. The patients had early onset in infancy and were mainly characterized by growth retardation.

Table 2
CLCNKB gene analysis results of patients with BS type 3.

	Status	Variant	Position	Type of mutation	ACMG classification	Reference
Case 1	Compound heterozygous	c.1312C > T (p.R438C) c.226C > T (p.R76X)	Exon 4 Exon 3	Missense Nonsense	Pathogenic Pathogenic	[9] [6]
Case 2	Compound heterozygous	c.226C > T (p.R76X) Exon 1–19 deletion	Exon 3 Exons 1–19	Nonsense Gross deletion	Pathogenic Pathogenic	[6] [20]
Case 3	Compound heterozygous	Exon 2–20 deletion c.1660_1667delAGCATCA (p. Ser554Hisfs*5)	Exons 2–20 Exon 16	Gross deletion Frameshift	Pathogenic Pathogenic	[21] [8]
Case 4	Compound heterozygous	c.1298G > A (p.G433E) **c.100 + 1 (IVS2) C > T**	Exon 14 Intron 2	Missense Splice-site	Likely Pathogenic Pathogenic	[22] Novel

Laboratory examination revealed hypokalemia, hypochloremia, elevated urinary potassium and chloride, metabolic alkalosis, hyperreninemic hyperaldosteronism but normal blood pressure, which confirmed the clinical diagnosis of BS. All participants carried a compound heterozygous mutation in the *CLCNKB* gene, which was genetically classified as BS type 3.

To date, >200 pathogenic mutations have been identified in the *CLCNKB* gene, including missense mutations, nonsense mutations, splice-site mutations, frameshift mutations, exon deletion mutations, whole-gene deletions, and insertion mutations. In Fig. 1 we summarised the mutation spectrum in *CLCNKB* gene of different countries [5–7,14,15,23–38]. Large deletions were the most common. Our study identified seven pathogenic mutations (Table 2), six of which have been reported previously [6,8,9,20–22]. Two cases carried large deletion mutations. According to the research of Han Y et al [38], large deletion mutations in the *CLCNKB* gene are very common, accounting for about 55% in China. However, nonsense mutations and frameshift mutations were more common in Korea and Japan. Missense mutations were more frequent in America and Spain. Splice-site mutations in *CLCNKB* gene were relatively rare. The c.100 + 1 (IVS2) C > T splice-site mutation has not been reported previously in the literature. According to the American College of Medical Genetics and Genomics guidelines, this is a pathogenic mutation. The splice-site mutation may lead to incorrect recognition and catalysis by restriction endonucleases, causing aberrant gene transcription, translation, and protein function. In this study, two cases carried the c.226C > T mutation, which led to the p.R612X amino acid mutation, causing premature protein translation termination. A minigene splicing assay was performed to validate the effect of this nonsense mutation. This mutation can lead to abnormal RNA splicing, skipping of exon 2 during transcription, and a lack of transmembrane helices in the CLC-Kb channel protein [39].

Clinically, BS type 3 is heterogeneous and may present with cBS, aBS, and Gitelman-like syndrome. The clinical variability of BS type 3 may be due to the wide expression of ClC-Kb in the TAL, DCT, and collecting duct. cBS is the most common phenotype. Approximately 44.5% of patients with BS type 3 present as cBS [40]. In our study, all patients fulfilled the clinical characteristics of cBS. The clinical manifestations of the four cases were infantile onset with moderate clinical symptoms such as failure to thrive, vomiting, and even incidentally detected hypokalemia. Hypochloremia is more pronounced in our study, as in the previous study [41]. Urinary calcium in classic BS is highly variable, ranging from hypocalciuria to hypercalciuria. Urinary calcium is usually normal. A previous study [42] showed that 20% of patients had hypercalciuria and 8% had hypocalciuria. The remaining patients had normal urinary calcium. Our 4 patients had no hypercalciuria. This confirms that normal urinary calcium is most common. On the other hand, this may be due to the small sample size. None of the patients had clinical features of aBS, including prenatal onset with polyhydramnios, low birth weight, severe dehydration, hypercalciuria and nephrocalcinosis. In addition, the participants had no hypocalciuria and mild

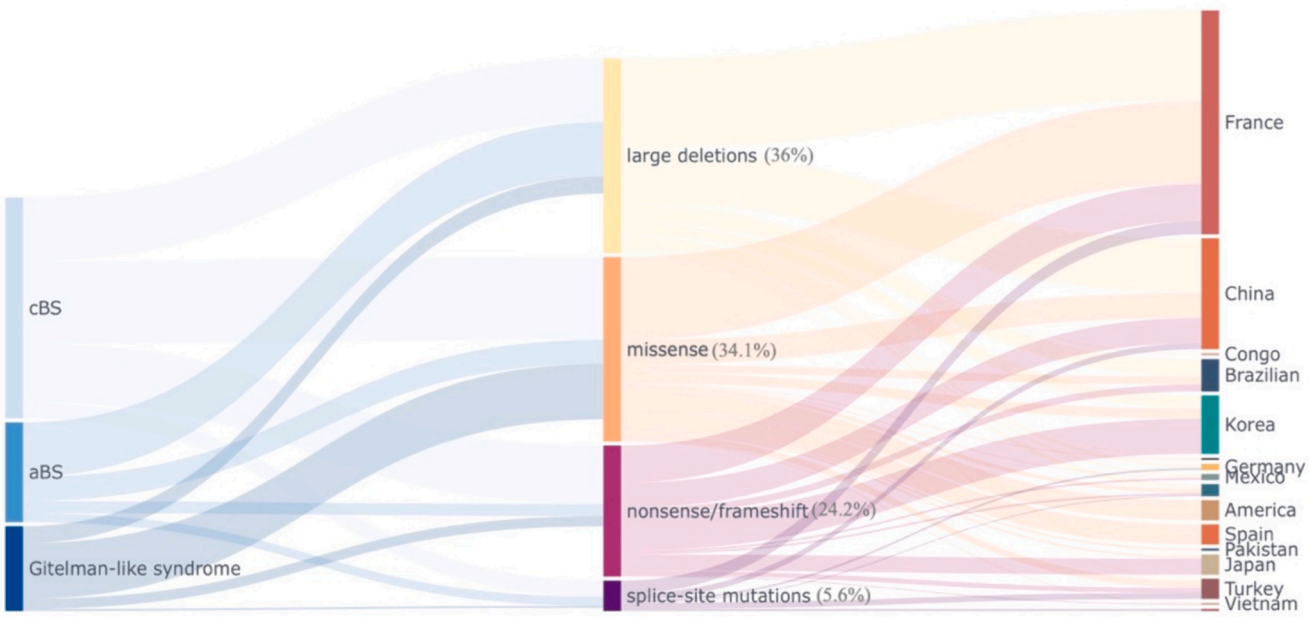

Fig. 1. Description of phenotypic and genotypic characteristics of BS type 3. Clinically, BS type 3 can present with cBS, aBS and Gitelman-like syndrome. cBS is the most common phenotype (left node). The forms of gene mutations are mainly including deletion mutations, missense mutations, nonsense mutations, frameshift mutations and splice-site mutations. Large deletion mutations in the *CLCNKB* gene are very common. Splice-site mutations in the *CLCNKB* gene were relatively rare (middle node). The mutation spectrum in the *CLCNKB* gene differs from countries (right node).

hypomagnesemia (indicating Gitelman-like syndrome phenotype).

The correlation between the genotype and phenotype of BS type 3 was controversial. The genotype-phenotype association studies revealed that severe mutations (large deletions, frameshift, nonsense, and essential splicing) and missense mutations may cause early onset of the disease and might have severe phenotypes [38,40]. Our patients carried variant kinds of mutation, including truncating mutations (nonsense mutations, frameshift mutations and large deletions) and nontruncating mutations (missense mutations). All patients presented with moderate clinical symptoms. In our study, as in the Spanish and Korean cohorts [5,43], the phenotypic association was not obtained with respect to the genotype. Truncated mutations such as nonsense mutations, frameshift mutations and large deletions may not be associated with the severe phenotype. However, our study had limitation due to the small sample size. More large sample studies are still required.

During the follow-up, growth and development should be monitored. It is not easy to maintain normal blood potassium. The target level for plasma potassium may be 3 mmol/L. [4] Chronic kidney disease is the most common complication. With long-term formal treatment, children with BS type 3 have a good prognosis and gradually improve in terms of growth, development, and symptoms while retaining normal renal function. The complication of renal dysfunction is significantly lower in BS type 3 than in other types of BS. In a Spanish cohort study involving 15 patients with BS type 3, height was average. Hypokalemia was almost universal but improved significantly compared with the initial diagnosis, during a mean follow-up period of 18.6 ± 9.4 years. In addition, renal function was primarily normal, except for three patients with proteinuria, two of whom showed mild renal impairment [43]. In a recent study from Korea, 33 children with BS type 3 were followed up for a mean of 8 years (range, 0.5–27 years), 12% of whom developed renal dysfunction [5]. Thus far, no large-scale, long-term follow-up studies have been conducted in China. All children in our study were treated with oral potassium chloride and indomethacin. Two cases were followed up for 15 years. All cases showed significant improvement in clinical and laboratory parameters. In addition, no nephrocalcinosis or renal dysfunction was observed, giving supporting evidence that BS type 3 had a good prognosis.

5. Conclusions

In conclusion, this study summarised the clinical characteristics of four Chinese children with BS type 3. Seven gene mutations were identified. The splice-site mutation c.100 + 1 (IVS2) C > T is novel, which enriches the domestic database of mutations underpinning BS. The clinical manifestations of BS type 3 mostly presented as cBS. Growth retardation is a common manifestation. The long-term prognosis was good. The limitation of this study was the small number of cases. we derived a result by analysing our data and the data of the previous study. There are various CLCNKB gene mutations, with deletion mutations being the most common.

CRediT authorship contribution statement

Yurong Piao: Writing – original draft, Investigation, Formal analysis, Conceptualization. **Congli Chen:** Visualization, Methodology. **Di Wu:** Supervision. **Min Liu:** Resources, Data curation. **Wenjing Li:** Resources. **Jiahui Chen:** Data curation. **Yanmei Sang:** Writing – review & editing, Conceptualization, Funding acquisition, Project administration.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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