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Long-Term Indomethacin Treatment in a Chinese Child with Gitelman Syndrome: Case Report and Literature Review on its Efficacy and Tolerance

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Data Interpretation D
Manuscript Preparation E
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Patient: Male, 4-year-old
Final Diagnosis: Gitelman syndrome
Symptoms: Short stature and growth retardation
Clinical Procedure: —
Specialty: Nephrology

Objective: Rare disease

Background: Gitelman syndrome (GS) is a rare inherited autosomal recessive salt-losing renal tubulopathy. Early-onset GS is difficult to differentiate from Bartter syndrome (BS). It has been reported in some cases that cyclooxygenase (COX) inhibitors, which pharmacologically reduce prostaglandin E2(PGE2) synthesis, are helpful for GS patients, especially in children, but the long-term therapeutic effect has not yet been revealed.

Case Report: A 4-year-old boy was first brought to our hospital for the chief concern of short stature and growth retardation. Biochemical tests demonstrated severe hypokalemia, hyponatremia, and hypochloremic metabolic alkalosis. The patient's serum magnesium was normal. He was diagnosed with BS and treated with potassium supplementation and indomethacin and achieved stable serum potassium levels and slow catch-up growth. At 11.8 years of age, the patient showed hypomagnesemia and a genetic test confirmed that he had GS with compound heterozygous mutations in the *SLC12A3* gene. At the age of 14.8 years, when indomethacin had been taken for nearly 10 years, the boy reported having chronic stomachache, while his renal function remained normal. After proton pump inhibitor and acid inhibitor therapy, the patient's symptoms were ameliorated, and he continued to take a low dose of indomethacin (37.5 mg/d divided tid) with good tolerance.

Conclusions: Early-onset GS in childhood can be initially misdiagnosed as BS, and gene detection can confirm the final diagnosis. COX inhibitors, such as indomethacin, might be tolerated by pediatric patients, and long-term therapy can improve the hypokalemia and growth retardation without significant adverse effects.

Keywords: Gitelman Syndrome • Cyclooxygenase Inhibitors • Bartter Syndrome, Type 3

Abbreviations: **BS** – Bartter syndrome; **COX** – cyclooxygenase; **DCT** – distal convoluted tubule; **GI** – gastrointestinal; **GS** – Gitelman syndrome; **HCT** – hydrochlorothiazide; **NCC** – sodium-chloride cotransporter; **PGE2** – prostaglandin E2

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/941627

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Background

Gitelman syndrome (GS, OMIM 263800) is an inherited salt-losing tubulopathy caused by loss-of-function mutations in the *SLC12A3* gene encoding the sodium-chloride cotransporter (NCC) in the distal convoluted tubule (DCT) and can mimic classic Bartter syndrome (BS) caused by mutations in the *CLCNKB* gene [1]. It was traditionally thought to be a relatively benign and late-onset disorder, but the clinical differentiation of GS from BS is not always easy, because hypomagnesemia and hypocalciuria are not always present [1]. Patients with GS are traditionally treated by oral potassium and magnesium supplementation and potassium-sparing diuretics. Several case series studies indicated that a nonselective inhibitor of cyclooxygenase (COX), such as indomethacin, which was recommended for use in BS patients [2], can also improve hypokalemia and developmental delays [3-5] in GS patients. Our previous study established elevated prostaglandin E2 (PGE2) levels in patients with genetically confirmed GS and provided reliable evidence for the application of COX inhibitors in GS patients [6]. The long-term effect of indomethacin in GS patients is unknown, and there is always a concern about the adverse effects, especially gastrointestinal (GI) tolerability and impairment of renal function [7], and self-discontinuation was common, which discouraged the clinical application.

We report a case of a Chinese boy who was first clinically diagnosed with BS and finally genetically diagnosed with GS. He was treated with long-term indomethacin and his growth retardation improved. Combined with a review of the relevant literature, this report may contribute to a deeper understanding of GS therapy.

Case Report

A 4.8-year-old boy presented to our hospital because of a 2-year history of short stature and growth retardation, with no other clinical manifestations, such as fatigue, muscle spasms, tetany, or palpitations (**Table 1**). In the past 10 months, his height had increased by only 3 cm. His maternal history, birth history, feeding history, and family history showed no abnormalities. His parents were healthy and non-consanguineous; the pregnancy, delivery, feeding, and neonatal course were uneventful. His mental and psychomotor development levels were normal for his age. As a child, he had no reported history of food or drug allergies, and no oral diuretics or catharsis drugs were taken previously. Nocturia (2 to 4 times per night) and enuresis occurred often before 4 years of age, but no polyuria was observed. On physical examination, his blood pressure was normal (95/65 mmHg), his weight was 13 kg, and his height was 97 cm (<P3, **Figure 1**).

After admission, biochemical tests demonstrated severe hypokalemia (K^+ 2.23 mmol/L), hyponatremia (Na^+ 122 mmol/L) and hypochloremic (Cl^- 93 mmol/L) metabolic alkalosis (pH 7.494, HCO_3^- 25 mmol/L, BE 3.1 mmol/L). The patient's serum magnesium was normal (0.87 mmol/L). His blood urea nitrogen (BUN) levels, creatinine (Scr) levels, and urinalysis results were also normal. The 24-h urinary potassium was 69 mmol/24 h (fractional excretion 41.2%), which indicated an increased urinary potassium level. The 24-h urinary calcium was 0.21 mmol/24 h, and the urine calcium: creatinine (Uca/cr) ratio was 0.12 mmol: mmol. The upright plasma renin activity and angiotensin II and aldosterone level were all significantly increased. Other serum cortisol and adrenocorticotropic hormone and growth hormone levels were in the normal range. Electrocardiogram, echocardiography, urinary Doppler, and adrenal Doppler ultrasound did not appear abnormal.

Saline solution and a large amount of potassium were given orally and intravenously as initial treatment. The patient's hyponatremia and hypochloremia quickly improved, but his hypokalemia was not relieved (2.7-3.1mmol/L). On the 4th day, spironolactone was added at a dose of 3-5 mg/kg/d. The serum potassium level then increased to 3.0-3.2mmol/L within 2-3 days. According to his early age of onset, the clinical manifestations, and the blood biochemical analysis of normomagnesemia, he was clinically diagnosed with BS. His parents refused to undergo genetic testing. Then, indomethacin was used to improve his hypokalemia at an initial dose of 15 mg bid. Soon, his serum potassium level increased to 4.0-4.5 mmol/L. Although the dose of potassium supplementation subsequently decreased and spironolactone was withdrawn, his serum potassium level remained normal.

Over the next 5 years, he showed a good response to indomethacin with a stable serum potassium level and slow catch-up growth (height increased to P3-10, weight to P25; **Figure 1**). His serum potassium level was sometimes low, but it could rise to normal when the dose of potassium supplementation and indomethacin was increased (up to 75 mg/d divided tid). At 11.8 years of age, while undergoing routine inspection, the patient's blood test showed hypomagnesemia (Mg^{2+} 0.54-0.6 mmol/L), which had never been found before. No other symptoms were reported. Then, the patient underwent a genetic test, which showed compound heterozygous mutations in *SLC12A3* gene and confirmed the final diagnosis of GS. Potassium-magnesium aspartate was taken orally to maintain normal magnesium levels. For its prolonged application and to avoid further adverse effects, indomethacin was slowly reduced to 50 mg/d at the age of 12.8 years. At that time, both his height and weight were up to P25-50 (**Figure 1**). During regular follow-up, his blood potassium levels fluctuated steadily between 3.1 and 4.0 mmol/L and his serum creatinine was in the normal reference range (**Table 1**).

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Table 1. Clinical data of the patient over a 10-year period.

Parameter/data	4.8 yrs (baseline)	9.8 yrs	11.8 yrs	12.8 yrs	14.8 yrs	Normal range
Weight (kg)	13	30	39	52	62	–
Height (cm)	97	131	149	154	161	–
Blood pressure (mmHg)	95/65	95/53	112/78	102/64	110/64	–
Blood routine test						
White blood cell count ($\times 10^9$/L)	6.4	5.7	6.21	3.61	5.8	4~10
Red blood cell count ($\times 10^{12}$/L)	5.0	5.1	5.36	5.20	5.36	3.5~5.5
Hemoglobin (g/L)	130	140	161	158	160	120~160
Platelets ($\times 10^9$/L)	298	302	160	289	342	100~300
Blood gas						
pH	7.494	7.46	7.47	7.406	7.456	7.35~7.45
Serum bicarbonate (mmol/L)	25	28.4	28	27.1	28	22~27
BE (mmol/L)	3.1	4.9	4.2	2.8	4.2	-4~2
Serum electrolytes (mmol/L)						
Sodium	122	137	136	140	139	135~145
Potassium	2.23	3.44	3.17	3.61	3.25	3.5~5.5
Magnesium	0.87	0.66	0.54	0.63	0.62	0.66~1.00
Calcium	2.28	2.44	2.32	2.32	2.48	2.25~2.74
Serum creatinine (umol/L)	31	42.2	47.5	62.4	56.9	35.9~73.5
Urine routine test	Neg	Neg	Neg	Neg	Neg	–
urine Ca/Cr (mmol: mmol)	0.12	0.018	0.016	0.005	0.003	<0.21
urine Pro/Cr (mg/ml: mg/ml)	0.2	0.14	0.13	0.11	0.09	<0.2
24 h urine potassium (mmol/d)	69	50.9	–	169	77.6	<25
24 h urine protein (mg/d)	88	76.38	–	130	112	<150
eGFR(ml/min/1.73 m^2)[1]	110	112	113	89	101.79	90~120
CCR(ml/min/1.73 m^2)[2]	126	119	116	95	123.2	90~120

yrs – years old; Neg – negative; BE – residual base; Ca/Cr – calcium/creatinine ratio; Pro/Cr – protein/creatinine ratio; eGFR – estimated Glomerular Filtration Rate; CCR – Creatinine Clearance Rate.
[1] eGFR was calculated from Schwartz formula. eGFR=”k”* height(cm)/serum creatinine(umol/L), k=36.5. The unit was ml/min./1.73 m^2.
[2] CCR=(Urine Cr*Urine Volume*1.73)/(Serum Cr*60*24*body surface).

At the age of 14.8 years, when indomethacin had been taken for nearly 10 years, the boy reported having moderate chronic stomachache, especially after meals. Reducing the dose of indomethacin did not relieve the pain. He had no nausea, vomiting, diarrhea, hematemesis, or melena. He was re-admitted to our hospital and further blood test results were almost normal except for hypokalemia, hypomagnesemia, and alkalosis. The serum creatine was 56.9 mmol/L and eGFR was 101.79 ml/min. The creatinine clearance (Ccr) was 123.2 ml/min/1.73 m^2 and 24-h urinary total protein was 112.32 mg. Results of a routine stool test and abdominal ultrasound were normal. His blood pressure was 110/64 mmHg, and his myocardial enzyme, electrocardiogram, echocardiography, and urinary Doppler results were also normal. The gastroduodenoscopy showed chronic superficial gastritis and slight bile regurgitation. After proton pump inhibitor (omeprazole) and acid inhibitor (aluminium

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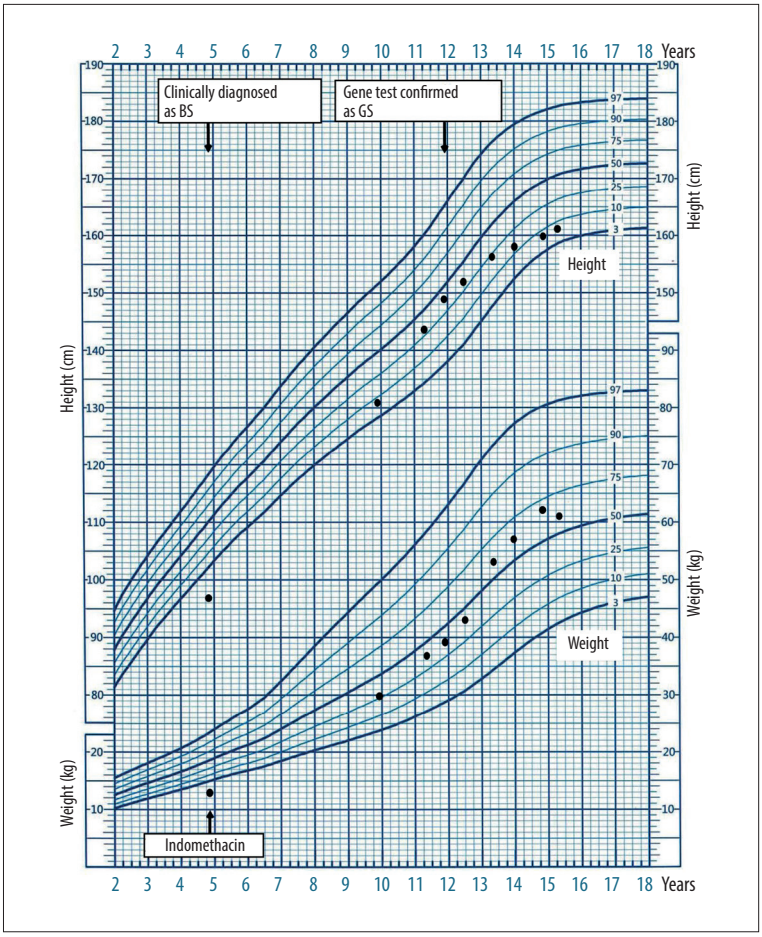

Figure 1. Timeline and growth curve of the patient compared to the standardized growth chart. The standardized growth chart for Chinese male children and adolescents aged 2 to 18 years was modified from Chin J Pediatr, 2009;47(7):487-92.

phosphate gel) therapy, his symptoms improved. Considering the moderate treatment effect and potential adverse effect, spironolactone was not chosen by the parents and he continued to take a low dose of indomethacin (37.5 mg/d divided tid).

Literature Review

We entered the keywords "Gitelman syndrome" and "indomethacin" in the PubMed, Wanfang, and SinoMed websites to search matched Chinese and English articles from 1999 to 2022. Following screening, 16 papers that reported GS patients treated with indomethacin were selected [3-5,8-20]. The main information and points are listed in **Table 2**. In most cases, the dose of indomethacin for adult patients was 25-150 mg/d [5,8-12,14-17,20], while it was 1-5 mg/kg/d for children [3,4,13,19]. There was a clear increase in the plasma potassium concentration, but the magnesium levels increased only slightly. Only 4 of the 16 papers reported adverse effects of indomethacin in GS patients [4,5,8,11]. Gastrointestinal (GI) intolerance (usually abdominal discomfort, heartburn, dyspepsia, or gastric irritation) was the most common problem, which was reported by 20-25% of the patients and resulted in early discontinuation. Blanchard et al reported that indomethacin (75 mg/d for 6 weeks) can cause decreased eGFR [5]. Larkins [3] and Schmidt [19] both reported children treated with indomethacin for more than 5 years, but did not report adverse effects.

Discussion

We report the case of a child with early-onset who was initially diagnosed with BS and later was confirmed to have GS by gene detection. With long-term indomethacin therapy for more than 10 years, his hypokalemia and growth retardation were both improved (**Table 1**). Indomethacin was well-tolerated, and there were no severe adverse effects. We also reviewed the literature to obtain a comprehensive understanding of indomethacin treatment in GS patients.

GS and BS patients have some overlapping clinical characteristics that make the diagnosis difficult, so genetic testing is the criterion standard for differentiating GS and BS. Because of the cost of genetic testing, the clinical diagnostic strategy for GS is always the preliminary choice in practice, and a careful history-taking, physical examination, and laboratory evaluation

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Table 2. Literature review of applications for Gitelman syndrome patients.

Year	Nation	Type	Main points	Author	Ref.
2019	China	Retrospective study (8/16 pts used indomethacin)	Treatment with triamterene or indomethacin(50-100 mg/d) significantly increased serum potassium concentration. Two patients (25%) stopped the treatment due to intolerance (one for abdominal discomfort and another for sleepiness)	Cui Y	[8]*
2015	French	Open-label, randomized, crossover study (30 pts)	Indomethacin (75 mg/d for 6 weeks) was the most effective but can cause gastrointestinal (GI) intolerance and decreased eGFR. Indomethacin caused GI intolerance (heartburn, dyspepsia, or gastric irritation) in 6 patients (20%), resulting in early discontinuation	Blanchard, A	[5]
2015	China	Case report (a 48-year woman with proteinuria)	Indomethacin (150 mg/d) treatment significantly increased serum potassium concentration and no adverse effects were mentioned	Zeng D	[9]*
2015	China	Cases (Two sisters, 42 and 37 years old)	Two sisters had inappetence and pain after indomethacin (25 mg/d) treated for 1-2 weeks. Their symptoms were relieved after stopping indomethacin	Ji W	[10]*
2014	Caucasian	Cases (two sisters)	Both children were treated with indomethacin (2-3.8 mg/kg/d) resulting in improved linear growth and polyuria. They were treated for 5-7 years but no adverse effects were reported	Larkins N	[3]
2013	China	Retrospective study (4/11 used indomethacin)	The symptoms of GS patients were relieved by supplementation with potassium alone or in combination with indomethacin (25-150 mg/d). Self-discontinuation was common in follow-up	Yang C	[11]*
2012	China	Retrospective study (4/17 pts used indomethacin)	Indomethacin (75 mg/d), spironolactone, and other potassium-magnesium asparaginase helped to relieve the symptoms. No adverse effects or long-term outcomes were mentioned	Qu L	[12]*
2011	China	Retrospective study (1/4 pts use indomethacin)	All symptoms resolved after treatment with potassium or combined magnesium supplementation, indomethacin (1.5-2.5 mg/kg), spironolactone, and captopril. Hypokalemia was corrected but hypomagnesemia was not	Fan S	[13]*
2010	Turkey	Case report (mental retardation)	Indomethacin and triamterene were administrated and helped the plasma levels of magnesium and potassium normalization	Tuhta GA	[14]
2006	China	Retrospective study (6/9 pts used indomethacin)	Treatment combination with indomethacin (75-150 mg/d) helped to improve hypokalemia. Serum magnesium levels were still lower than normal range	Yang GQ	[15]*
2005	China	Case report (a 63-year-old woman)	GS may be present with severe hypocalcemia and hypokalemic periodic paralysis; the combined use of indomethacin (50 mg tid) with triamterene has good therapeutic effect	Ran XW	[16]*
2003	China	Case report (39-year-old man)	Indomethacin (25 mg tid) treatment significantly increased serum potassium concentration	Tao H	[17]*

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Table 2 continued. Literature review of applications for Gitelman syndrome patients.

Year	Nation	Type	Main points	Author	Ref.
2002	Israel	Case report	Rofecoxib instead of indomethacin promptly elevated serum potassium concentration with normalization of plasma aldosterone and near normalization of renin. Rhabdomyolysis was also ameliorated by COX 2 inhibition	Mayan H	[18]
2001	Germany	Cases report| (3/5 children used indomethacin)	Indomethacin (1-2 mg/kg/d) failed to fully correct hypokalemia and hypomagnesemia, but markedly improved growth velocity and normalized IGF-1 levels in the 3 patients with short stature. For the longest, indomethacin was treated for 7 years. The adverse effects were not mentioned	Schmidt H	[19]
2001	Japan	Case report (20-year-old man)	Treated with potassium, spironolactone, and indomethacin for over 9 years, no abnormal signs. The adverse effects were not mentioned	Tsuchiya H	[20]
1999	Europe	Cases report (3 sisters)	Hypotension and polyuria were eliminated by taking 2 mg/kg/day indomethacin. Increasing the indomethacin dose to 4 mg/kg/day improved their growth significantly, without changing their symptoms or biochemistry. Gastrointestinal hemorrhage was reported in the oldest sister while on high-dose indomethacin (5 mg/kg/d)	Liaw LC	[4]

pts – patients; * paper in Chinese.

should be undertaken. Late-onset, hypomagnesemia, and hypocalciuria are features that differentiate GS from BS [21], but in recent years, with the development of sequencing technology, cases with normomagnesemia, normocalciuria, or early-onset GS have been reported [22,23]. The renal tubular function test was also proven to be effective in differentiation [24]. In our previous study [25], we evaluated the diagnostic utility of hypomagnesemia, hypocalciuria, and the hydrochlorothiazide (HCT) test in Chinese GS patients. We found that the sensitivity, specificity, and area under the curve (AUC) for hypomagnesemia and hypocalciuria were not sensitive enough to diagnose GS, but the HCT test was significantly superior (AUC 1.000, 95% CI 0.905-1.000). As we previously reported [22], normomagnesemic GS patients showed milder clinical manifestations, electrolyte abnormalities, metabolic alkalosis, and NCC dysfunction than the hypomagnesemic patients. It was also reported [26] that hypomagnesemia was not present at the early stage of GS, but presented years later. In this study, the child showed hypomagnesemia in the 7th year of disease and presented some challenges for the clinical diagnosis. We speculate that normomagnesemia might be a feature of the early-onset GS in children. Further study is needed to investigate the intensive mechanism involved in the association between the phenotype and genotype.

Growth retardation is an important comorbidity of renal tubular disease in children [1]. Clinical studies have demonstrated growth hormone deficiency in children with primary renal tubular disease, and laboratory data showed tissue-specific alterations in growth hormone and insulin-like growth factors-1 in hypokalemic animal models [27]. Maintaining a good electrolyte and acid-base balance can help promote catch-up growth. For this child, the only chief concern was growth retardation. Actively seeking medical attention helped him to receive an early diagnosis and intervention and finally improved his growth. The heights of his mother and father were 151 cm and 168 cm, respectively. At the age of 15, his height was 161 cm and almost reached his target height (166±8.5 cm). Both the child and his parents were satisfied with the treatment. Therefore, early diagnosis and treatment are important for improving the growth and prognosis of these children.

For treatment, when potassium and magnesium supplementation are not sufficient for persistent hypokalemia, potassium-sparing diuretics and renin angiotensin system blockers can be used. The most available and commonly used potassium-sparing diuretics was spironolactone, while its antiandrogenic effects were highly concerning in children and young adults, such as gynecomastia, hirsutism, erectile dysfunction, and menstrual irregularities [1]. In addition, spironolactone can aggravate the renal salt wasting and cause hypotension. In this case, spironolactone was taken at the early stage of disease but failed to improve the hypokalemia. The parents also worried about the adverse effects. For these reasons, when GS

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diagnose was made or when the GI complications appeared, they were preferred to maintain indomethacin instead of trying spironolactone again.

The application of COX inhibitors in GS and BS patients relied on the mechanism of elevated PGE2 levels. Existing evidence indicates that increased PGE2 might be secondary to salt loss rather than completely due to the primary disease. Even in BS, a traditional hyperprostaglandin E syndrome, not all patients show enhanced synthesis or excretion of PGE2 [28]. Our previous study [6] showed that the urinary PGE2 concentration varied in each individual and exhibited good correlation with serum chloride, serum magnesium, urinary calcium excretion, and arterial HCO_3^- concentration. GS patients with higher PGE2 showed higher percentages of nocturia and dyspnea, more severe metabolic alkalosis, a higher daily urinary excretion of potassium, and more severe NCC dysfunction. This provided reliable evidence for the application of COX inhibitors in GS patients. Larkins et al found increased urinary prostaglandin (PGE2) excretion in 2 children who showed a good response to indomethacin [3]. In this study, although we did not measure the level of PGE2, from the relieved clinical manifestations (severe hypokalemia and growth retardation), we supposed increased PGE2 levels in the child. For personalized therapy, we suggest that doctors measure PGE2 and its metabolite levels before treatment, and COX inhibitor may be a more appropriate choice for patients with elevated PGE2 levels.

The adverse effects of COX inhibitor can never be ignored. To the best of our knowledge, the most frequent adverse effect of COX inhibitors is gastrointestinal (GI) tolerability; mucosal injury in the upper GI tract is common with long-term use and affects up to 70% of long-term users [29]. According to the literature review, NSAIDs are rarely used and reported in GS patients. Only 4 studies reported the adverse effects of indomethacin, which were all regarding GI intolerance, at a proportion of 1/4 to 1/3. The longest treatment duration was reported by Tsuchiya [20], who treated a man with indomethacin for 9 years, but the dose and adverse effects were not mentioned in the paper. In our study, the GS patient was treated with indomethacin for more than 10 years and showed good tolerance to the treatment, with only a slight stomachache. We can get more insight from reports of other diseases. Gasongo et al [30] analyzed the treatment of 19 children with BS from 1994 to 2016 (mean age at diagnosis was 0.9 months). In terms of adverse effects, a 2-year-old child developed necrotizing enterocolitis after 7 days of medication and then was treated again 6 months later and reported no adverse reactions. Two children with BS developed gastritis after 3 months of therapy. In the latest consensus and recommendations for BS [31], NSAIDs were recommended for use in early childhood, and gastric acid inhibitors were recommended for use together with NSAIDs. However, they also mentioned that the risks of gastrointestinal and cardiovascular adverse effects need to be considered individually, especially if these medications are used in the first few weeks or months. The other important adverse effect of COX inhibitors is renal impairment. The medical literature reveals many adverse effects of NSAIDs on the kidneys, such as acute kidney injury (AKI), tubulointerstitial nephritis (TIN), nephrotic syndrome, and chronic kidney disease (CKD) [32]. Blanchard et al [5] reported that indomethacin significantly reduced eGFR by 10.0 ml/min/1.73 m^2 after 6-week treatment. The influence of long-term NSAIDs treatment on renal function was reported in a cohort of children with juvenile idiopathic arthritis [33]. For those been treated by only NSAIDs, the cumulative proportion of patients free from kidney injury at 240 months from disease onset was 100%, indicating acceptable risk of long-term drug use. In this case, at age 14.8 years old, when indomethacin had been taken for nearly 10 years, the patient's kidney function (**Table 1**) remained normal. His myocardial enzyme, electrocardiogram, and echocardiography were all normal, which reflected normal heart function. Because patients with risk factors of kidney impairment have far greater risk of adverse effects [34], it was recommended to create an individualized medication strategy for patients to control the nephrotoxicity. As mentioned before, we suggest a COX2 inhibitor as a more appropriate choice for patients with elevated PGE2 levels.

Conclusions

In conclusion, early-onset GS in childhood can be initially misdiagnosed as BS, and gene detection can confirm the final diagnosis. COX inhibitors, such as indomethacin, might be tolerated by pediatric patients, and long-term therapy can improve hypokalemia and growth retardation without significant adverse effects.

Ethics Approval

This study involving human participants was reviewed and approved by the Research Ethics Committee of Children's Hospital Affiliated to Capital Institute of Pediatrics.

Acknowledgments

We thank the patient and his family for their participation.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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