A Case Report: Gitelman Syndrome or Bartter Syndrome?

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Case report

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Abstract

Background: Gitelman syndrome (GS) is a rare autosomal recessive inherited tubular disease which is caused by mutation in the SLC12A3 gene. It is characterized by hypokalemic alkalosis with hypomagnesemia and hypocalciuria, and can cause serious complications such as arrhythmia, syncope, sudden death, etc. Bartter syndrome (BS) is similar to Gitelman syndrome in clinical and laboratory examinations. If lack of sufficient understanding of the disease, it is easy to cause misdiagnosis and missed diagnosis.

Case presentation: A 6-year-old Chinese girl presented with history of hand and foot spasms and was diagnosed with hypokalemia. Although multiple symptomatic treatments of potassium supplementation was given, is the concentration of potassium was still at a low level. Gene analysis revealed that the presence of two heterozygous mutations, i.e. a missense mutation c.248G> A and a frameshift mutation c.2875_2876del, in the SLC12A3 gene.The child was diagnosed with Gitelman syndrome(GS) due to SLC12A3 compound heterozygous mutation. Through treatment, the level of ion metabolism in children remains stable.

Conclusions: By reviewing its clinical characteristics and diagnosis and treatment ideas, we can help improve clinicians' understanding of children's GS.

1. Background

Gitelman syndrome (GS) is a renal tubular disease caused by a defect in the sodium-chlorine transporter, with an approximate incidence of 1/40,000[1]. It belongs to the autosomal recessive inheritance and is also known as familial hypokalemia and hypomagnesemia. Its clinical manifestations include hypokalemia and Chlorine alkalosis, hypomagnesemia, hypouricemia, normal or low blood pressure and activated renin-angiotensin-aldosterone system symptoms [2]. Due to persistent hypokalemia, when there are gastrointestinal diseases, the QT interval can be prolonged, which may cause arrhythmia, syncope, and sudden death[3]. Since the incidence of GS is low, there are fewer reports in Chines patients, especially in children. Type III Bartter syndrome (BS) caused by mutations in the *CLCNKB* gene is similar to GS in clinical and laboratory examinations. Both of the two diseases have hypokalemia, renal potassium loss, low chloride metabolic alkalosis, RAAS activation but low blood pressure. However, BS usually has an early onset age and severe clinical symptoms, while, GS tends to have relatively mild symptoms and a late onset age. Therefore, the main manifestations to distinguish GS from BS are the age of onset, the presence of low urinary calcium, low blood magnesium, and whether it is combined with growth retardation[4]. Genetic testing can confirms diagnosis. Most clinicians still lack sufficient knowledge of this disease, which can easily lead to misdiagnosis and missed diagnosis.

2. Case Presentation

A 6-year-old Chinese girl was admitted to the community hospital because of discovered hypokalemia for 6 days and hand and foot spasms for half a day. Six days ago, the patient was examined in a local hospital for "lame" symptoms. Blood biochemistry indicated hypokalemia and hypomagnesemia. After multiple symptomatic treatments of potassium and magnesium supplementations, the symptoms of lameness improved, but potassium and magnesium ions were still at low levels. Half a day before administration into community hospital, the patient developed hands and feet spasms, accompanied with difficulties in moving the knuckles and restricting the arms and legs. During this period, the child was conscious, and the blood potassium and magnesium were 2.3 mmol / L and 0.44 mmol / L, respectively. No family history of similar diseases has been identified. In addition, since the onset of the disease, the bowel movements were normal and no vomiting occurred. There was no abnormality detected in bilateral adrenal, cardiac, and urinary ultrasound examinations. ECG: 1. Sinus rhythm 2. Long QTc interval. Blood gas analysis: pH 7.478 pO2 53 mmHg pCO2 35.2 mmHg BE 2.4 mmol/L. Blood potassium fluctuated between 2.85–3.12 mmol/L (normal value: 3.5–5.3 mmol/L), blood magnesium fluctuated between 0.48–0.71 mmol/L (normal value 0.75–1.02 mmol/L), and blood chlorine fluctuated 97.1–99.6 mmol/L (normal value: 99–110 mmol/L). 24-hour urine potassium: 39.76 mmol/L (normal value: 25.00–125.00 mmol/L), 24-hour urine calcium 1.64 mmol/L (normal value: 2.50–8.00 mmol/L), calcium/creatinine ratio (Ca/Cr) was 0.18. Renin-angiotensin II-aldosterone system (RAAS): Angiotensin II (A II) 103.64 ng/L (normal value: 23.00–75.00 ng/L), periplasmal renin activity (PRA) 1.66 ng/L (normal value: 0.13–1.74 ng/L), aldosterone (ALD) 387.59 ng/L (normal value: 30.00–180.00 ng/L). In this case, the main manifestation of the child was hand and foot spasm. The blood potassium and blood magnesium were measured repeatedly, and the effect of symptomatic treatment with potassium supplementation and magnesium supplementation failed to improve the condition. Combined with the characteristics of metabolic alkalosis, refractory hypokalemia, hypomagnesemia, hypocalciuria, normal blood pressure, RAAS activation, Gitelman syndrome or Bartter syndrome should be considered. Hypomagnesemia and hypouria calcium further indicated Gitelman syndrome for clinical diagnosis. Genetic testing was then applied in this case (Table 1). Whole exon sequencing analysis revealed the presence of two heterozygous mutations in the SLC12A3 gene, c.248G > A (nucleotide 248 of the coding region was mutated from guanine to adenine), leading to amino acid changes p.R83Q Amino acid 83 was mutated from arginine to glutamine), which was a missense mutation. According to the pedigree verification analysis, the heterozygous mutation at this locus was identified in the patient’s father (Fig. 1). The other mutation of SLC12A3 in this patient was c.2875_2876del, which was a grameshift mutation caused by amino acid changes p.R959Sfs * 11.The mother's heterozygous mutation at this locus was detected. (Fig. 2) Since the diagnosis of Gitelman syndrome was clear, Captopril (6 mg tid), spironolactone tablets (20 mg bid), oral potassium supplementation, and magnesium supplementation were then treated symptomatically. The symptoms of hand-foot spasms were relieved in the patient. Blood magnesium fluctuated from 0.72 to 0.95 mmol/L.

3. Discussion And Conclusions

Gitelman syndrome (GS) is an autosomal recessive disease caused by inactivation of mutations in the SLC12A3 gene. It is characterized by hypopotassic metabolic alkalosis, hypomagnesemia, and hypouricemia [5]. Approximate 140 different mutations in *SLC12A3* has been associated to the pathogenesis of GS, including insertion mutations, splicing mutations, and missense mutations [6]. GS can manifest as a variety of clinical symptoms. Mild symptoms include fatigue, nocturia, muscle weakness, while patients with severe symptoms can show hand-foot convulsions, paralysis, rhabdomyolysis, epilepsy, or fatal arrhythmia. Long-term complications can lead to calcification and choroidal calcification [7, 8]. Consumption of potassium and magnesium will prolong the duration of action potentials in cardiac muscle cells , which will subsequently lead to prolongation of QT interval in about 50% of children and increase the risk of arrhythmia [3]. This shows that the clinical manifestations of children with GS are mostly non-specific symptoms. Therefore, children diagnosed with GS have a large misdiagnosis rate and missed diagnosis rate [9].

In the diagnosis of GS, it is necessary to distinguish it from Bartter syndrome (BS). In particular, type III Bartter syndrome caused by a mutation in the *CLCNKB* gene is similar to GS in clinical and laboratory tests, both of which have hypokalemia, renal potassium loss, hypochlorite metabolic alkalosis, RAAS activation, and normal blood pressure. However, other types of BS usually have an earlier age of onset and severe clinical symptoms. Relatively, GS is mild and has a late age of onset. Therefore, the main points of identification are the age of onset, the presence of hypocalcemia, hypomagnesemia, and whether they have combined delayed development[4]. Although a few children with severe hypokalemia and hypomagnesemia may have growth retardation, the the growth and development of patients with GS are generally not affected.

The diagnosis of GS depends on clinical symptoms and laboratory tests. According to the consensus and guidance on Gitelman syndrome published in 2016 and the "Consensus of Experts in Diagnosis and Treatment of Gitelman Syndrome" published in 2017, the biallelic mutation of the *SLC12A3* gene was used as diagnostic criteria [7,10]. This patient had hypokalemic metabolic alkalosis, hypomagnesemia, hypochloremia, hypocalciuria, RAAS activation, normal blood pressure, calcium/creatinine ratio <0.2, and no abnormalities in urinary ultrasound, consistent with GS clinical manifestations. Combined with genetic diagnosis, we found two heterozygous mutations in *SLC12A3* gene, which further validates the diagnosis of Gitelman syndrome. The main pathogenic gene in GS is *SLC12A3*, which encodes a thiazide-sensitive Na^+-Cl^-cotransporter (NCC) located on the apical membrane of the first part of the renal tubules [11]. Genetic screening of this patient revealed genetic mutations at two loci: c.248G> A (nucleotide 248 of the coding region was mutated from guanine to adenine), resulting in an amino acid change of p.R83Q (amino acid number 83 by The arginine mutation is glutamine), which was a missense mutation; the other mutationwas c.2875_2876del, which was a frameshift mutation and resulted in the amino acid change to p.R959Sfs * 11. The above mutations are preliminarily determined to be pathogenic mutations according to the ACMG guidelines, which have been recorded in the HGMD (The Human Gene Mutation Database) database. At the same time, the parents of the children were genetically sequenced. It was

found that the parents carry different site mutations of the *SLC12A3* gene, and the proband was a heterozygous mutation.

Although no effective cures for GS are currently availble, most patients have a good prognosis. In some cases, delayed growth and development may be caused by severe hypokalemia and hypomagnesemia. The main purpose of current treatments is to correct electrolyte disorders, reduce clinical symptoms. Individualized lifelong oral potassium and magnesium supplements are the main treatment for patients with GS. When persistent symptomatic hypokalemia occurs, potassium supplementation can be used together with potassium diuretics, renin angiotensin system blockers, or non-steroidal anti-inflammatory drugs [12,13,14]. In this case, the child had hypokalemia and hypomagnesemia that were difficult to correct by oral potassium and magnesium supplementation. Therefore, according to the guidelines, potassium diuretics and renin angiotensin system blockers were administrated at the same time. At the time of discharge, the blood potassium was 3.90 mmol/L and the blood magnesium was 0.72 mmol/L.

To sum up, this case report systematically analyzes the clinical and laboratory examination characteristics of children with GS.In addition, gene sequencingconfirms GS caused by *SLC12A3* complex heterozygous mutations. Combined with previous domestic and foreign reports on GS, we believe that current case report of patient's clinical characteristics, diagnosis and treatment ideas will improve clinicians the understanding of children's GS, thereby reducing the rate of misdiagnosis and missed diagnosis.

List Of Abbreviations

GS Gitelman syndrome

BS Bartter syndrome

Ca/Crcalcium/creatinine ratio

RAASRenin-angiotensin II-aldosterone system

A IIAngiotensin II

PRAperiplasmalrenin activity

ALDaldosterone

NCCNa^+-Cl^-cotransporter

HGMD The Human Gene Mutation Database

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the institutional review board, The GuangDong Women and Children Hospital. After explanation of the possible consequences of the study, written informed consent was obtained from all study participants.

Consent for publication

Consent for publication of the case was obtained for each participant, including case description, clinical data and images.Written consent to publish this information has been obtained from the parents of the study participant.

Availability of data and materials

The data and materials that support the findings of this study are available on request from the corresponding author [HHS]. The data are not publicly available due to them containing information that could compromise research participant privacy/consent.

Competing interests

The authors declare that they have no competing interest.

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Authors' contributions

YBW and JJH wrote the manuscript. HHS and BW supervised the management of the case and approved the manuscript. DXY managed the patient and finalized the manuscript. HZ and QQT performed the genetic studies. All authors read and approved the final manuscript.

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Tables

Table 1

Key points for GS and BS identification

	Gitelman syndrome	Bartter syndrome
Smilarities	Hypokalemia, metabolic alkalosis, RASS activation, normal or low blood pressure	
Differences		
Age of onset	Latechildhoodor adulthood	After birth or preschool
Clinical symptoms	Symptoms mild	symptoms obvious, may be severe polydipsia, polyuria and dehydration, and even developmental disorders or delay
Urinary calcium	low	high
Furosemide load test	+	-
Dihydrocarbazide load test	-	+
gene testing	*SLC12A3* gene mutation	*CLCNKB* gene mutation

Figures

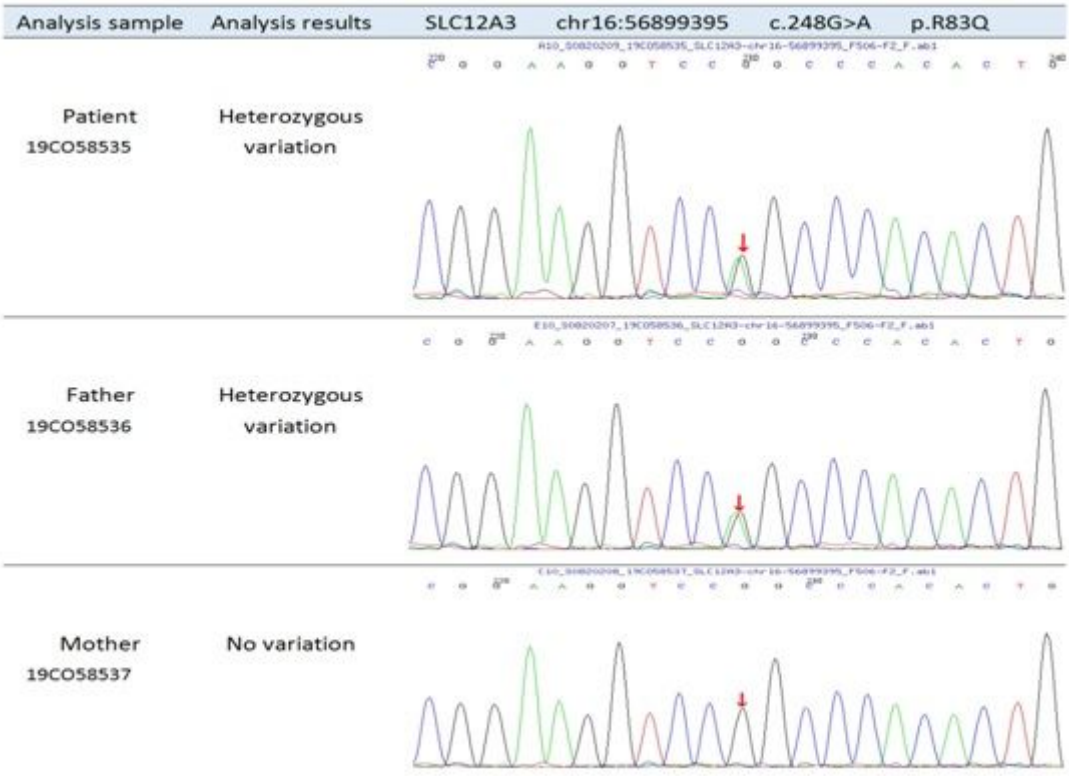

Figure 1

C.248G> A mutation

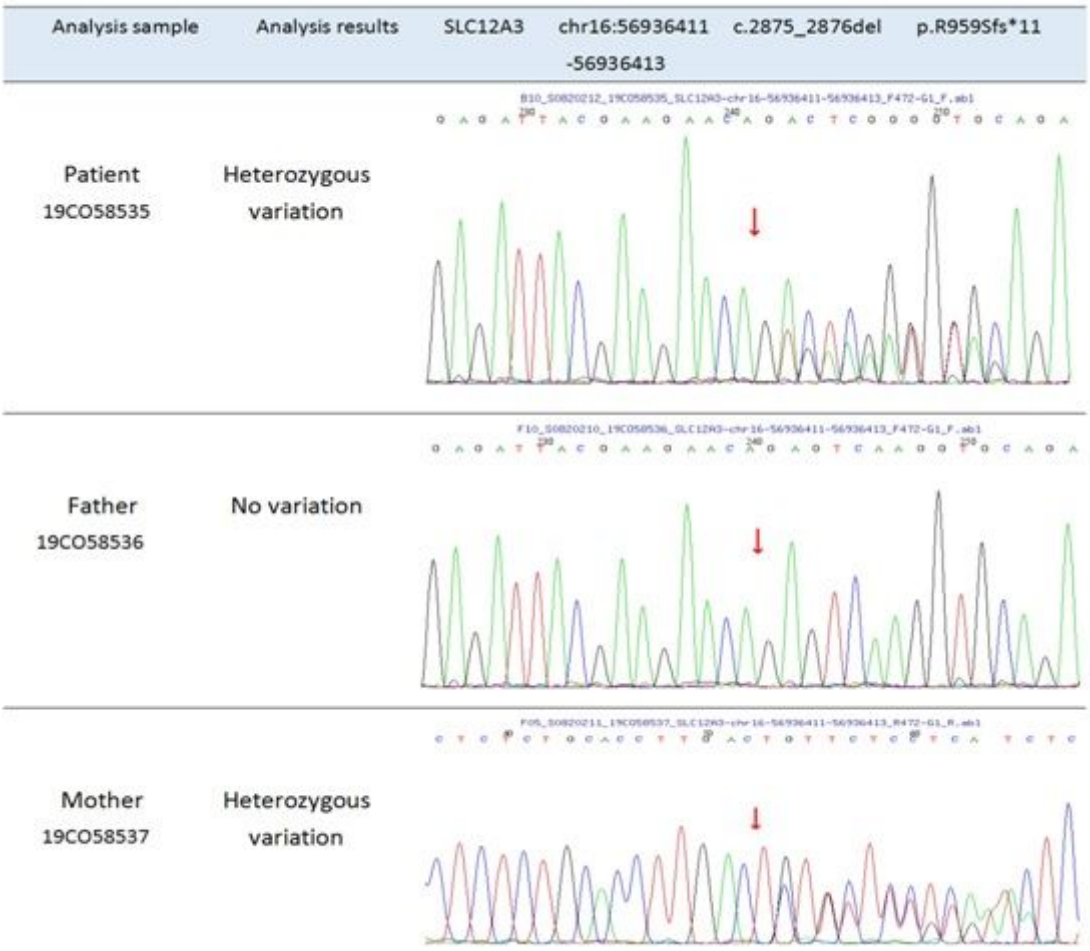

Figure 2

C.2875_2876del mutation

Supplementary Files

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- CAREchecklistEnglish2013.pdf