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Case Report

# Hypokalemic Metabolic Alkalosis with Normal Blood Pressure in a Male Patient-A Case Report

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## Abstract

Hypokalemic metabolic alkalosis with normal blood pressure is a group of autosomal recessive tubulopathies that include Gitelman, Bartter and EAST syndromes. Gitelman syndrome is more common in the general population, and gene variants are known to cause the syndrome. All mentioned tubulopathies are treated symptomatically - by replacement of electrolytes excreted through urine, which can be carried out orally or parenterally. Also, electrolyte correction can be attempted with cyclooxygenase inhibitors or potassium-sparing diuretics, but this type of therapy is used in case of intolerance to oral supplements. The long-term prognosis for these patients is mostly favourable, except in the case of type one and antenatal type of Bartter syndrome with sensorineural deafness. In this paper, a case from clinical practice is presented with an algorithm that established the diagnosis of Gitelman syndrome with its subsequent confirmation by genetic analysis.

**Keywords:** Bartter Syndrome; EAST Syndrome; Gitelman Syndrome; Hypokalemic Metabolic Alkalosis, Next Generation Sequencing

## Introduction

A group of disorders with hypokalemic metabolic alkalosis and normal blood pressure includes several hereditary tubulopathies: Gitelman Syndrome (GS), Bartter Syndrome (BS) and EAST syndrome. These are rare disorders with an incidence of 1:100000 in the general population [1]. These disorders are caused by variantsgenes that encode various protein transporters important for the reabsorption of sodium, potassium and chloride in the renal tubules [2]. Although GS and various types of BS exhibit many of the same clinical symptoms, their underlying causes differ. The associated proteins are located in distinct parts of the nephron, leading to different pathophysiological mechanisms and compensatory responses to their loss of function [3].

## Gitelman Syndrome

GS is an autosomal recessive tubular disorder with a prevalence of 1:40000, which makes it the most common tubulopathy in the general population [1,4]. It was initially thought to be a subtype of BS, given the similar clinical presentation with hypokalaemic, hypochloraemic metabolic alkalosis, but was established as a separate entity by molecular genetics. It is characterized by metabolic alkalosis, hypokalemia, hypomagnesemia hypocalciuria and hyperreninaemia with normal blood pressure [5]. GS is caused by variants of the SLC12A3 gene encoding the thiazide-sensitive Na-Cl Cotransporter (NCCT) expressed in the apical membrane of epithelial cells in distal convoluted tubules. Most patients are compound heterozygous but it is common for patients to be affected by only a single variant in SLC12A3 gene [6]. There is a loss of Sodium (Na) and Chloride (Cl) through the urine, which consequently leads to hypovolemia and secondary activation of the Renin-Angiotensin-Aldosterone System (RAAS). Hypocalciuria

occurs due to increased reabsorption in the proximal tubules due to hypovolemia. In this syndrome, there is also a variant of the TRPM6 gene that encodes the claudin 6 cation channel important for the transport of Magnesium (Mg) in the distal tubule, resulting in hypermagnesiuria and hypomagnesemia [1,2,5-14]. The presence of both hypocalciuria and hypomagnesemia is highly predictive for GS, although hypomagnesemia may be absent. The onset of symptoms occurs during adolescence or adulthood and its clinical course is milder compared to BS. Symptoms usually occur in puberty or even during adulthood [2]. Patients often report muscle weakness, salt craving, polyuria, syncopeparesthesias, tetany and carpopedal spasms [1,6,8,15]. There is also nocturia, increased thirst, late onset of puberty, palpitations and joint pains [6-8,15]. Chondrocalcinosis can develop later in life [1,7]. A case of GS with nephrocalcinosis due to the deposition of calcium phosphate in the kidneys has also been described. The formation of these deposits could be due to the reduced solubility of calcium phosphate caused by long-term hypomagnesemia. Another cause of lower solubility of calcium phosphate could be the simultaneous presence of a tubulointerstitial lesion and long-term hypokalemia [12].

### Bartter Syndrome

BS is an autosomal recessive disorder of electrolyte reabsorption in the thick ascending limb of the loop of Henle important for calcium reabsorption which occurs passively, through paracellular claudin pathways [1]. BS has traditionally been categorized into neonatal and classic forms. Neonatal BS is a severe type that presents antenatally, causing significant polyuria. This can result in polyhydramnios, premature delivery, and severe electrolyte and water loss [16]. The classic form presents more subtly, typically in early childhood, and is characterized by polyuria, polydipsia, volume contraction, and muscle weakness [17]. Currently, BS is classified into six subtypes based on the underlying genetic causes. Furthermore, these subtypes can be grouped into three categories based on the similarity of the main molecular mechanisms in which the encoded proteins participate and their associated pathophysiology: BS types 1 and 2; BS types 3 and 4; and BS type 5 [18]. Bartter Syndrome Type 1 (BS1) is caused by mutations in the gene encoding the luminal NKCC2 transporter, leading to polyhydramnios and premature birth. Patients with BS1 typically exhibit hypercalciuria and nephrocalcinosis.

Bartter Syndrome Type 2 (BS2) is caused by mutations that disrupt the function of the luminal KCNJ1 channel, leading to polyhydramnios and prematurity. Patients with BS2 also exhibit hypercalciuria and nephrocalcinosis. Additionally, children with this type of BS often experience transient hyperkalemia during the neonatal period, as KCNJ1 is a major pathway for potassium secretion in the collecting duct [19]. Bartter Syndrome Type 3 (BS3) is sometimes referred to as "classical BS" because patients with this subtype typically present postnatally, aligning more closely with Bartter's original description. BS3 is caused by a defective function of the basolateral chloride channel CLCNKB. Bartter Syndrome Type 4a (BS4a) is caused by mutations in the gene encoding Barttin, a subunit of the basolateral chloride channels CLCNKA and CLCNKB. Type 4b (BS4b) is caused by simultaneous mutations in the genes encoding both CLCNKA and CLCNKB, resulting in a phenotype similar to BS4a. Children with BS4 (either a or b) typically present with polyhydramnios and premature birth, and thus can also be classified as having "antenatal BS." Patients may exhibit hypercalciuria, nephrocalcinosis, and hypomagnesemia. Both subtypes of BS are associated with sensorineural deafness, as both chloride channels and their Barttin subunit are expressed in the inner ear, where chloride efflux through these channels is necessary for hair cell depolarization. Deafness occurs only if the function of both types of chloride channels is impaired, significantly hindering chloride transport, which is the case in BS4 but not in BS3, where chloride transport via CLCNKA remains intact [20]. Finally, autosomal dominant or familial hypocalcemia can be associated with hypokalemic, hypochloremic metabolic alkalosis. Prior to the discovery of MAGED2 mutations, this condition was sometimes referred to as Bartter Syndrome Type 5 (BS5). However, it is now recognized as a Bartter-like subform of familial hypocalcemia. This condition is caused by an activating mutation in the gene encoding the basolateral calcium-sensing receptor (CaSR) [21].

### East Syndrome

EAST syndrome is an extremely rare, autosomal recessive disorder caused by variants in the KCNJ10 gene that encodes for basolateral Potassium Channels (KCN), and the tubulopathy is identical to that of GS. It also includes epilepsy, ataxia and sensorineural deafness.

## Diagnosis

Distinguishing between GS and the various types of BS based solely on symptoms is currently challenging and often inaccurate. There is significant overlap in phenotype between GS and the different types of BS, and considerable clinical variability can exist even among individuals with the same syndrome. Typically, a prenatal presentation of BS would exclude BS3; however, in some instances, BS3 can also present early or prenatally [22]. Given the significant phenotypic variability within and between families affected by these syndromes, along with the diverse range of symptoms that often complicate diagnosis, genetic studies represent a critical and conclusive diagnostic tool for GS and BS. Identifying causal variants in associated genes not only confirms the diagnosis but also aids in establishing a more accurate prognosis and developing effective treatment strategies for patients [22, 23]. Moreover, genetic information can provide insights into potential comorbidities associated with these syndromes. From a public health perspective, genetic studies also serve as the foundation for prenatal and preimplantation diagnostics. Prenatal testing is particularly relevant for BS types 1, 2, 4, and 5, especially in cases presenting with polyhydramnios without morphological anomalies,

which should raise suspicion for BS and prompt consideration for genetic testing [17]. While most patients with BS and GS now receive a genetic confirmation of their diagnosis, a significant subset of patients with a BS phenotype do not have identifiable disease-causing variants. New techniques such as whole-exome/genome sequencing offer promise in identifying additional genes responsible for BS and GS, thereby advancing our understanding of tubular solute handling mechanisms [19,24]. For example, recent findings have highlighted vesicle-associated membrane protein 3 (VAMP3) as crucial for the accurate intracellular trafficking of NKCC2 to the luminal membrane; Vamp3-/- mice exhibit a BS phenotype, suggesting VAMP3 as a potential candidate gene [25]. Additionally, mutations affecting the phosphorylation of NKCC2 could impair its function. Adenylyl Cyclase 6 (AC6), critical in vasopressin-mediated NKCC2 phosphorylation, has been implicated in a mouse model where Ac6 deficiency led to reduced NKCC2 expression and a mild BS phenotype, making AC6 another intriguing candidate gene for unresolved BS cases [26]. Furthermore, not all cases involve novel disease genes; for instance, we reported a patient clinically diagnosed with GS who was found to have a mutation in HNF1B [27].

## Treatment

Our understanding of tubular transporters and the factors influencing their expression is rapidly expanding. However, this knowledge has not yet significantly impacted the treatment of patients with tubulopathies. The treatment of BS and GS remains purely symptomatic. Considering that there is a loss of salt in GS and BS, it is important to compensate for this loss with the oral intake of salt [1,2]. There is still no relevant scientific research to support this claim. Vasopressin enhances sodium reabsorption through the transcellular pathway by upregulating NKCC2 expression and activity [26]. Recently, it has been found that vasopressin may also augment sodium uptake through the paracellular pathway, potentially involving claudin 10b [28]. The implications of these new insights into paracellular sodium transport for exploring treatment options for BS are yet to be fully understood. For now, this compensation method is more intuitive, especially since many patients have a pronounced desire for salty foods. Also, there are oral preparations of NaCl that can be administered in a dose of 2,4 g to 4,8 g per day in divided doses [29]. With antenatal BS, parenteral compensation with the use of a physiological solution is sometimes necessary [1,9,29]. All other electrolytes have to be compensated by the intake of supplements, which refers to the intake of potassium chloride as well as magnesium in the case of GS. The targeted value for potassium replacement should be 3.0 mmol/L. It is also preferable for the

supplementation to be in the form of potassium chloride since chlorine is the main anion lost in GS which contributes to alkalosis. Oral potassium supplements often cause side effects such as nausea, vomiting, diarrhoea and even peptic ulcers. Therefore, it is recommended to take them with food. The initial daily dose of potassium chloride for oral supplementation should be at least 40 mmol [29]. In addition to potassium chloride, an alternate source of potassium can be food such as various fruits, vegetables, fish, meat, chocolate, fruit juices and cereals. It is important to remember that when preparing vegetables, there is a significant electrolyte loss due to boiling and rinsing water [6,9,29]. Moreover, the increased intake of electrolytes could, due to the increase in serum concentration, cause additional loss of the same electrolytes through the tubules, which may require even greater compensation. Consequently, if large doses are involved, complications such as diarrhoea or ulcer disease are possible [1]. The mentioned complications can further increase the loss of necessary electrolytes. Therefore, supplements should be taken divided into smaller doses, several times a day [6,29]. Magnesium can also be replenished through foods such as fish, whole grains, green leafy vegetables, especially nuts, chickpeas, dark chocolate and bananas. Magnesium supplements in the form of organic salts (aspartate, citrate, fumarate) are recommended in favour of inorganic salts because their bioavailability is higher. The initial daily dose should be 300 mg per day, divided into several doses [6,13,29]. Proton pump inhibitors should be avoided in patients with magnesium supplement therapy because they interfere with the gastrointestinal absorption of magnesium [30]. Cyclooxygenase (COX) inhibitors, such as indomethacin (1-3 mg/kg/24h), and potassium-sparing diuretics, such as spironolactone and amiloride, can also be administered [1,6,9]. Recently, an animal study demonstrated successful gene therapy targeting the NKCC2 gene using an adenoviral vector delivered directly to the TAL in vivo via renal artery injection, thus avoiding hepatic uptake. Specific promoters were employed to direct vectors to their designated nephron segments, resulting in co-expression of exogenous and endogenous NKCC2 in the TAL [31]. This represents a potential initial step towards gene therapy as a potential curative treatment for tubulopathies such as BS and GS. However, extensive research is necessary to ensure the long-term safety of viral vectors and to achieve permanent transfection of the target gene in specific cell types, ultimately resulting in functional transporter restoration. Moreover, certain recurrent variants in the KCNJ1 gene lead to protein misfolding, causing retention in the endoplasmic reticulum and subsequent degradation via the ER-associated degradation pathway. These folding defects have been corrected at low temperatures in yeast cells, a promising development reminiscent of successful correction of similar defects in cystic fibrosis using chaperone proteins [32-34]. Therefore, exploring methods to correct KCNJ1 folding defects and restore protein function warrants further investigation and may offer a new therapeutic approach for a specific subset of BS patients.

## Prognosis

Since the clinical manifestation of subtypes of BS are different and include the entire spectrum of electrolyte imbalances, the outcomes

are difficult to predict. Progressive chronic kidney damage is usually observed in BS3 and BS4. However, it is important to note that adequate regulation of electrolyte imbalance should lead to clinical improvement [1]. GS has a milder clinical course and does not lead to impairment of renal function. However, it is sometimes difficult to distinguish GS from both the milder forms of BS and mixed forms of these two syndromes.

## Case Report

### Clinical Data

The patient, born in 1991, is otherwise healthy and does not take any chronic therapy. In December 2020, he was treated on an outpatient basis for pneumonia. During the treatment, hypokalemia was accidentally found in laboratory findings. Furthermore, potassium values were periodically controlled and were mostly between 2,6 mmol/L and 3.1 mmol/L. He reported no complaints, eats normally, and has a good appetite. He does not take laxatives. From the family history, it is important to note that the patient has a first cousin who is being treated for proven GS. The findings listed in Table 1 stand out from the nephrological examination. From the presented findings, it is clear that the patient has a mild metabolic alkalosis with hypokalemia, and according to the findings of the KMAT, normotension. Furthermore, it is important that in addition to hypokalemia, hypomagnesemia and hypochloremia are present, and that the 24-hour urine test shows the loss of the mentioned electrolytes via kidney excretion. To confirm the loss of salt through the tubules, the Excretion Fraction Of Chlorine (FeCl) was calculated, the values of which prove the aforementioned mechanism of salt loss. Among the mentioned findings, hypocalciuria is the main difference between GS and BS. As stated earlier, in GS, we expect reduced excretion of calcium in the urine due to hypovolemia and increased calcium concentration in the proximal tubule, and thus increased reabsorption of calcium in the proximal tubule. The loss of calcium through the tubules, in addition to the absolute value of calcium in the 24-hour urine, can also be expressed through the ratio of calcium to creatinine in the urine. In this case, this finding is in favour of hypocalciuria and GS. Among the other findings, it is important to state that the presented patient has a normal renal function with a normal value of creatinine clearance.

| LABORATORY PARAMETERS | REFERENCE VALUES | PATIENT I.N. |
|---|---|---|
| Na (s) | 137- 146 | 139 |
| K (s) | 3.9- 5.1 | 2.5- 3.1 L |
| Ca (s) | 2.02- 2.60 | 2.44 |
| Cl (s) | 97.0- 108.0 | 90.3 L |
| Mg (s) | 0.65- 1.05 | 0,62 L |
| Blood pH | 7.350- 7.460 | 7.39- 7.43 |
| HCO3 | 21- 25 | 26.8- 27.5 H |
| Renin (p) | lying 4.2- 59.7 mU/L | 196.7 |
| | standing 5.3- 99.1 mU/L | |
| Aldosterone (p) | lying < 859 pmol/L | 492 |
| | standing >1200 pmol/L | |
| eGFR | >60 ml/min/1.73m2 | 105 |
| Serum osmolality | 280- 300 mOsm/kg | 278 |
| Na (u) | 40- 220 mmol/24h | 350 H |
| K (u) | 25- 125 mmol/24h* | 67 H |
| Ca (u) | 2.50- 7.50 mmol/24h | 0.84 L |
| Cl (u) | 110- 250 mmol/24h | 252 H |
| Mg (u) | 3.0- 5.0 mmol/24h | 9 H |
| Ca/creatinine (u) | >0.2 | 0.083 L |
| FeCl | ≥ 0.5% | 2.79 H |
| ABPM | | |

eGFR – estimated glomerular filtration rate.

**Table 1:** Laboratory findings.

### Genetic Analysis

Subsequently, a genetic analysis using the Next Generation Sequencing (NGS) method was performed for a total of 39 genes included in Renal Tubular Disorders Panel. Using the mentioned method, two pathogenic, heterozygous variants in the SLC12A3 gene were found:

1. SLC12A3 c.1180+1 G>T (splice donor). This sequence change affects a donor splice site in intron 9 of the SLC12A3 gene. It is expected to disrupt RNA splicing. Variants that disrupt the donor or acceptor splice site typically cause loss of protein function (PMID: 16199547), and loss-of-function variants in SLC12A3 are known to be pathogenic (PMID: 20848653, 22009145, 25841442). Algorithms developed to predict the effect of sequence changes on RNA splicing suggest that this variant may disrupt the consensus splice site.

2. SLC12A3 c.1924 C>G (p.Arg642Gly). This sequence change replaces arginine, which is basic and polar, with glycine, which is neutral and non-polar, at codon 642 of the SLC12A3 protein (p.Arg642Gly). This missense change has been observed in individual(s) with Gitelman syndrome (PMID: 11408395, 12112667, 25422309). Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: "Deleterious"; PolyPhen-2: "Probably Damaging"; Align-GVGD: "Class C0"). For both variants, there is an entry in ClinVar (Variation ID: 437426 and 397523) and both are present in population databases (rs749098014, gnomAD 0,005% and rs200697179, gnomAD 0,007%). For these reasons, both variants have been classified as Pathogenic. The presented clinical data and the results of NGS analysis favour a diagnosis of GS. Therefore, the electrolyte replacement therapy was administered through oral supplements with beneficial results. Additionally, his mother (age 52) and sister (age 32) were tested with the same panel and reported positive for SLC12A3 c.1180+1 G>T variant without symptoms.

## Conclusion

GS, BS and EAST syndrome are inherited tubular disorders with hypokalemic metabolic alkalosis and normal blood pressure. It is often difficult, based on symptoms and laboratory findings, to diagnose the exact syndrome and its subtype. Since the treatment of individual electrolyte imbalances must be accurate and precise, an accurate diagnosis is indispensable. Genetic tests are considered the optimal tool for achieving an accurate and definitive diagnosis, despite the challenges they may present. Genetic analysis with sequencing methods can help in the diagnostic process, especially in cases where it is difficult to determine the exact syndrome due to the similarity of the symptomatology. With the right diagnosis, adequate therapy will be administered to the patient promptly. However, the prognosis for these syndromes remains poorly understood. Consequently, there is a significant need for population studies aimed at long-term follow-up of patients to improve our understanding of prognosis and outcomes.

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