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**Bartter and Gitelman syndromes: Spectrum of clinical manifestations caused by different mutations**

Shibli AA *et al*. Bartter and Gitelman syndromes

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**Abstract**

Bartter and Gitelman syndromes (BS and GS) are inherited disorders resulting in defects in renal tubular handling of sodium, potassium and chloride. Previously considered as genotypic and phenotypic heterogeneous diseases, recent evidence suggests that they constitute a spectrum of disease caused by different genetic mutations with the molecular defects of chloride reabsorption originating at different sites of the nephron in each condition. Although they share some characteristic metabolic abnormalities such as hypokalemia, metabolic alkalosis, hyperplasia of the juxtaglomerular apparatus with hyperreninemia, hyperaldosteronism, the clinical and laboratory manifestations may not always allow distinction between them. Diuretics tests, measuring the changes in urinary fractional excretion of chloride from baseline after administration of either hydrochlorothiazide or furosemide show very little change (< 2.3%) in the fractional excretion of chloride from baseline in GS when compared with BS, except when BS is associated with KCNJ1 mutations where a good response to both diuretics exists. The diuretic test is not recommended for infants or young children with suspected BS because of a higher risk of volume depletion in such children. Clinical symptoms and biochemical markers of GS and classic form of BS (type III) may overlap and thus genetic analysis may specify the real cause of symptoms. However, although genetic analysis is available, its use remains limited because of limited availability, large gene dimensions, lack of hot-spot mutations, heavy workup time and costs involved. Furthermore, considerable overlap exists between the different genotypes and phenotypes. Although BS and GS usually have distinct presentations and are associated with specific gene mutations, there remains considerable overlap between their phenotypes and genotypes. Thus, they are better described as a spectrum of clinical manifestations caused by different gene mutations.

**Key words:** Gitelman syndrome; Bartter syndrome; Potassium; Chloride; Magnesium; Metabolic alkalosis; Genetics

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**Core tip:** As inherited disorders of renal tubular excretion and reabsorption of electrolytes, Bartter and Gitelman syndromes were previously considered as genotypic and phenotypic heterogeneous diseases. Although they share some characteristic features, the clinical and laboratory manifestations may not always allow distinction between them. Different genetic mutations inducing impairment of electrolytes transport across different sites of the nephron have been reported in each condition However, considerable overlap exists between the different genotypes and phenotypes of these two conditions that are now better described as a spectrum of clinical manifestations caused by different gene mutations.

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**INTRODUCTION**

Bartter syndrome (BS) and Gitelman syndrome (GS) are inherited autosomal recessive conditions resulting in defects of renal tubular excretion and reabsorption of electrolytes. A brief reminder of the physiology of renal handling of water and electrolytes homeostasis is helpful to understand these two conditions.

**PHYSIOLOGY**[1]

Water and electrolyte homeostasis is maintained by kidney. To avoid significant losses of electrolytes in the urine following glomerular filtration, their reabsorption in the renal tubule is required. The distal nephron reabsorbs approximately 30% of the filtered sodium: while one quarter is reabsorbed in the thick ascending limb (TAL) of Henle’s loop; the distal convoluted tubule (DCT) and the cortical collecting duct (CCD) reabsorb 10%. Dysfunction of distal tubular functions, due to either genetic or acquired causes, will result in a clinical presentation specific to the affected part of the distal nephron.

The TAL is not permeable to water and reabsorbs a large proportion of the filtered sodium chloride, which leads to interstitial hypertonicity that powers the countercurrent exchange and urinary concentration mechanisms. In case of impairment of this function, a major loss of water and sodium occur, as seen with loop diuretics.

The DCT, composed of an early segment (DCT1), a late portion (DCT2), and the connecting tubule (CNT) leading to the CCD, finely regulates renal excretion of sodium chloride, calcium and magnesium. These segments express the different transport proteins involved in the reabsorption sodium, calcium and magnesium and their functional impairment leads to extracellular volume depletion, initially compensated for by hyper-aldosteronism and resulting in increased potassium urinary losses.

The total distal nephron has a finely regulated reabsorption capacity to cope with the intake and/or extrarenal losses of salt and water. The macula densa (MD) in the distal nephron modulates renal hemodynamics and tubular reabsorption with the modulation of the renin-angiotensin II system and intrarenal cyclo-oxygenase 2 (COX-2) activity regulating the glomerular arterial resistance.

**GENERALITIES**

Although BS and GS share some characteristic metabolic abnormalities such as hypokalemia, metabolic alkalosis, hyperplasia of the juxtaglomerular apparatus with hyperreninemia, hyperaldosteronism, and, sometimes hypomagnesemia[2-4], the clinical and laboratory manifestations may not always allow distinction between them[5]. They were previously considered as genotypic and phenotypic heterogeneous diseases, with urinary calcium and prostaglandin E excretion as well as serum magnesium levels enabling distinction between them. However recent evidence suggests that they constitute, instead, a spectrum of disease characterized by defective chloride reabsorption caused by different genetic mutations at different sites of the nephron in each condition, resulting in three major types of tubulopathy[1,6]: (1) Abnormality in the sodium-potassium-chloride cotransporter NKCC2 or the renal outer medullary potassium channel will lead to an impairment in the thick ascending limb of Henle which has a greater salt reabsorption capacity, resulting in severe polyuric loop dysfunction with major urinary salt and water losses. This condition is also known as antenatal BS or hyperprostaglandin E syndrome; (2)

Defects in the sodium-chloride cotransporter NCCT or the chloride channel ClC-Kb in the DCT which modulates urinary calcium and magnesium excretion, will induce hypokalemia (in BS) with hypomagnesemia in (GS); and (3) Abnormality in the chloride channels ClC-Ka and ClC-Kb or their beta-subunit Barttin in combined loop and distal convoluted tubule will lead to more manifestations (antenatal BS or hyperprostaglandin E syndrome with sensorineural deafness).

**CHARACTERISTICS SHARED BY BOTH CONDITIONS**

Both conditions are inherited in an autosomal recessive mode. Chronic hypokalemia results in fatigue, dizziness, constipation, muscle cramps and weakness. Although usually mildly symptomatic, hypokalemia can be exacerbated by fluid and electrolytes losses caused by diarrhea or vomiting, or by abuse of alcohol, cocaine or other drugs, and can lead to rhabdomyolysis, prolonged QT interval, life-threatening arrhythmia, syncope and sudden death[7,8].

Biochemical findings common to both conditions include hypokalemia, hypochloremia and metabolic alkalosis associated with hyperreninemia and hyperaldosteronism. Hypomagnesemia used to be considered a feature of GS; however, many reports have also described it in patients with BS[9,10].

**DISTINCTIVE CHARACTERISTICS OF BS**

The defect of NaCl reabsorption in the thick ascending limb of Henle's loop (TALH) is central to the pathophysiology of BS[3]. The condition has a prevalence of approximately 1.2 per million[11]. Severe failure to thrive commonly presents in early childhood. Blood pressure is usually normal. BS is classified into five subtypes corresponding to specific defective transport proteins in the renal tubules secondary to different gene mutations[12] as shown in Table 1.

***At the luminal (urinary) side of the terminal ascending loop***

BS type I or antenatal Bartter syndrome or hyperprostaglandin E syndrome. This autosomal recessive condition is caused by mutations of the *SLC12A1* gene coding the Na-K-Cl co-transporter protein in the renal tubule. Antenatal manifestations such as polyhydramnios secondary to fetal polyuria may occur. As transepithelial voltage gradient cannot be maintained to absorb calcium and magnesium, hypercalciuria and hypermagnesiuria occur and may result in nephrocalcinosis. There is no associated sensorineural deafness.

BS type II or neonatal Bartter syndrome with transient hyperkalemic metabolic acidosis or antenatal Bartter syndrome. This autosomal recessive condition is caused by mutations of the *KCNJ1* gene that codes the inward rectifying renal outer medullary potassium (ROMK) channel. The initial neonatal presentation is hyperkalemic, metabolic acidosis that may mimic pseudohypoaldosteronism. Antenatal manifestations such as polyhydramnios secondary to fetal polyuria may occur. There is no associated sensorineural deafness.

***On the basal lateral (blood) side of the terminal ascending loop***

The autosomal recessive BS type III or classic BS is caused by a defect in the chloride channel Kb (ClC-Kb) secondary to mutations encoding the basolateral chloride channel. As ClC-Ka chloride permeability is preserved, the symptoms are usually very mild but might overlap with those of GS because the ClC-Ka is also present in the DCT. Sensorineural deafness, nephrocalcinosis and nephrolithiasis do not occur.

The autosomal recessive BS type IV or antenatal BS with sensorineural deafness is due to *BSND* gene mutations leading to an altered Barttin β-subunit of both chloride channel Ka (ClC-Ka) and ClC-Kb needed for potassium chloride membrane localization. As both ClC-Ka and ClC-Kb channels are affected, the symptoms are usually severe and may initially mimic pseudohypoaldosteronism. However, when the renal outer medullary potassium channel (ROMK) and other potassium channels or transporters start to compensate, the neonates develop hypokalemia and metabolic alkalosis. The resulting disturbances in potassium transport cause the sensorineural deafness, because cochlear hearing function relies on several processes governing potassium flow such as its inflow into cochlear hair cells, its entry into hair cells by electro-chemical forces and its recycling either *via* KCNQ4 channels or by entering Deiter’s cells (*via* KCC3, KCC4)[13-15].

BS type V is an autosomal dominant condition caused by L125P mutations of the extracellular basolateral calcium sensing receptor (CASR) located on chromosome 16q13. This results in hypocalcemia hypercalciuria and suppression of parathyroid hormone function, associated with Bartter-like syndrome[16,17].

**DISTINCTIVE CHARACTERISTICS OF GS**

The autosomal recessive GS, or familial hypokalemic metabolic alkalosis with hypomagnesemia and low urinary calcium excretion has a prevalence of approximately 1 in 40000[18]. It results from transport defects located in the distal convoluted tubule (DCT) caused by mutations in the solute carrier family 12, member 3 gene (*SLC12A3*) that encodes the thiazide-sensitive NaCl cotransporter (NCC). Mutations in the gene encoding the chloride channel ClC-Kb have also been identified in some individuals[19].

GS is very often asymptomatic. If symptoms occur, this is usually after the age of six years but the condition is often diagnosed in adolescents or adults. The initial presentation is usually the incidental discovery of an asymptomatic and isolated hypokalemia. Some patients present with fatigue, dizziness, muscle weakness, cramps, vomiting, abdominal pain, fever, nocturia and polyuria. Facial Paresthesias may also occur and, occasionally, hypotension. Failure to thrive is not usually severe unless severe hypokalemia and hypomagnesemia are present. Hypocalciuria is a distinct feature and interstitial nephritis may develop because of the persistent hypokalemia. Adults can present with chondrocalcinosis with swollen and warm joints with overlying tenderness. Sudden cardiac arrest has been reported occasionally[8]. Hearing defect is absent. The most important differential diagnosis is BS (especially type III). Antenatal diagnosis is available but not usually required because most patients have a good prognosis[18].

**DISTINGUISHING BETWEEN THE TWO CONDITIONS**

***Clinical and biochemical findings***

The main differences in the clinical presentation of BS and GS are explained in Table 2[20]. Although the symptoms of BS type III (classical BS) often occur before the age of two, patients can present at any age until adolescence, with an initial history of polyuria and polydipsia, followed by growth retardation if the diagnosis and treatment were delayed[21]. Patients usually have high urinary prostaglandins E2 (PGE2) production and hypercalciuria[1,22]. However, the distinction between BS and GS is not always that simple because phenotypic variances. Although genetic diagnosis is possible, its use remains limited because it is costly and not always readily available. In addition, its usefulness remains limited because the “hot spot” mutations along the gene are not always present.

***Diuretics test: Response to thiazide and furosemide***

The diuretic test involves measuring the change in the urinary fractional excretion of chloride after administration of a diuretic. This consists of either oral hydrochlorothiazide (1 mg/kg up to 50 mg) or furosemide (a single dose of 2 mg/kg). The diuretic is administered after a 7-d “washout” period, during which therapies other than potassium and magnesium supplements are withheld. In GS caused by a defect is in the thiazide-sensitive NCCT, the thiazide test results in only a minimal change (< 2.3%) in the fractional excretion of chloride from baseline. In BS with ClC-Kb mutations, this blunted response does not occur but a normal response to furosemide exists. In BS with KCNJ1 mutations, there is a good response to both diuretics[23]. Because of a higher risk of volume depletion in infants or young children, diuretic tests are not recommended for them when they are suspected to suffer from BS. In patients with the normotensive hypokalemic alkalosis phenotype, an abnormal hydrochlorothiazide test allows to predict with a very high sensitivity and specificity the GS genotype and thus avoid the need for genotyping[24].

***Genetic investigations***

Clinical symptoms and biochemical markers of GS and classic form of BS (type III) may overlap and thus genetic analysis is required to make an accurate diagnosis[1]. Although genetic tests are available, they still face technical difficulties caused by large gene dimensions and the absence of hot-spot mutations. They are also lengthy and costly. Furthermore, considerable overlap exists between the different genotypes and phenotypes.

In most patients with GS, DNA variants are found in the thiazide-sensitive NaCl co-transporter (NCC) encoding *SLC12A3* gene. In others, variants in the chloride channel ClC-Kb encoding *ClC-Kb* gene are identified, causing not only classical BS (type III), but also other phenotypes that overlap with antenatal BS (Types I-II) or with GS[1,3,5,12,20,25-41]. Other genetic and/or environmental factors also act as effect modifiers in other cases of ClC-Kb mutation[29,30] and in polycystic kidney disease[31]. Furthermore, in one family sharing *ClC-Kb* variant some relatives presented clinical characteristics specific for GS, on the one side of the spectrum, to classic BS on the other[33]. As a result, screening for the *ClC-Kb* gene in patients with the GS phenotype who do not have variants in the *SLC12A3* gene is therefore required[10].

**TREATMENT**

***Bartter syndrome***

Hypokalemia, often in the range of 2-3 mmol/L, is caused by increasing urinary potassium losses due to the activation of the renin-angiotensin-aldosterone system and hyperaldosteronism secondary to salt and water depletion caused by the inability to reabsorb sodium in the TAL of the loop of Henle or the DCT. Correcting it is the mainstay of treatment.

Potassium chloride supplements are preferred salt because of the coexisting chloride deficiencies in these patients. Several hundred mmol of potassium per day may be required to correct the hypokalemia.

Spironolactone, a specific aldosterone antagonist, binds competitively binding to the receptors present at the aldosterone-dependent sodium-potassium exchange site in the DCT. It increases water excretion while retaining potassium.

By inhibiting sodium reabsorption at the DCT, cortical collecting tubule, and collecting duct, Amiloride reduces potassium and hydrogen excretion.

By interfering with the active transport exchange of potassium and sodium in the distal tubule, cortical collecting tubule, and collecting duct Triamterene decreases calcium excretion and increases magnesium loss.

Angiotensin-converting enzyme (ACE) inhibitors, such as captopril, enalapril and lisinopril, block the conversion of angiotensin I (ANG I) to ANG II and prevent the secretion of aldosterone from the adrenal cortex.

Nonsteroidal drug anti-inflammatory drugs (NSAID) decrease prostaglandin PGE2 synthesis, which causes the pressor resistance to ANGII and norepinephrine, hyperreninemia, and increased sympathoadrenal activity. The resulting hyporeninemic hypoaldosteronism leads to potassium retention. Medications include indomethacin and naproxen which decrease the activity of the enzyme cyclo-oxygenase (COX) which increases prostaglandin synthesis.

Administration of growth hormone (GH) is required for the treatment of short stature and growth failure, which are common.

In the presence of muscle spasms or tetany, calcium or magnesium supplements may be required.

***Gitelman syndrome***

Asymptomatic patients often require no treatment but need outpatient monitoring once or twice yearly. A high-sodium and potassium diet is recommended.

Lifelong magnesium supplementation is required. As high doses of magnesium cause diarrhea, normalization of serum magnesium level is difficult to achieve. Oral magnesium-chloride supplementation is initially started with a daily dose of 3 mmol/m2 or 4-5 mg/kg, divided in 3-4 administrations to avoid diarrhea. The dose will subsequently be adjusted according to serum magnesium levels. It has also to be increased during periods of intercurrent illness, especially in the presence of vomiting and diarrhea. If tetany develops, intravenous administration of 20% MgCl2 (0.1 mmol mg/kg per dose) should be administered and can be repeated every 6 hours if needed.

Hypokalemia may require large amounts of potassium chloride supplements, up to 10 mmol/kg in children and 500 mmol/d in adults, but poor gastric tolerance frequently occurs. If symptomatic, hypokalemia is treated by a combination therapy of amiloride (5–10 mg/1.73 m2 per day) and spironolactone (200-300 mg/d), in addition to KCl supplementation (1-3 mmol/kg per day divided in 3-4 doses). Amiloride therapy should be started with a lower dose initially to avoid the development of hypotension.

Symptomatic chondrocalcinosis (pseudo-gout attacks) requires non-steroidal anti-inflammatory drugs (NSAID).

**PROGNOSIS**

***Bartter syndrome***

The prognosis depends on the degree of the receptor dysfunction. Without treatment, there is significant morbidity and mortality. Once treated, most patients lead fairly normal lives. Nearly all patients have growth retardation and/or short stature, which improve with potassium, indomethacin, and growth hormone (GH) therapy. A small proportion of patients develops slow progression to chronic renal failure, due to interstitial fibrosis, and may require renal replacement therapy. Nephrocalcinosis may occur and is often associated with hypercalciuria. Cardiac arrhythmias, sometimes leading to sudden death, may occur when significant electrolyte imbalances are present. Sensorineural deafness, associated with Bartter syndrome IV, requires appropriate treatment.

***Gitelman syndrome***

The long-term prognosis is generally excellent. The musculoskeletal and constitutional symptoms, the nocturia and polydipsia, may seriously hamper the daily activities and negatively affect the patients’ quality of life. There is a risk of developing sudden cardiac arrhythmias, sometimes life-threatening, especially in the presence of severe hypokalemia, hypomagnesemia and alkalosis. These episodes are sometimes precipitated by non-adherence to therapy, the presence of concomitant diarrhea or vomiting or competitive sports that induce potassium and magnesium loss by sweating.

**CONCLUSION**

Although BS and GS usually have distinct presentations and are associated with specific gene mutations, there remains considerable overlap between their phenotypes and genotypes. Thus, they are better described as a spectrum of clinical manifestations caused by different gene mutations.

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|  |  |  |  |
| --- | --- | --- | --- |
| **Disorder** | **Gene affected** | **Gene product** | **Clinical presentation** |
| Bartter syndrome type I | *SLC12A1* | NKCC2 | Antenatal Bartter syndrome (Hyperprostaglandin E syndrome) |
| Bartter syndrome type II | *KCNJ1* | ROMK | Antenatal Bartter syndrome |
| Bartter syndrome type III | *ClC-Kb* | CLC-Kb | Hypochloremia, mild hypomagnesemia, failure to thrive in infancy |
| Bartter syndrome type IVA | *BSND* | Barttin (B-subunit of CLC-Ka and CLC-Kb) | Antenatal Bartter syndrome (Hyperprostaglandin E syndrome) and sensorineural deafness |
| Bartter syndrome type IVB | *ClC-Ka* and *ClC-Kb* | CLC-Ka and CLC-Kb | Antenatal Bartter syndrome (Hyperprostaglandin E syndrome) and sensorineural deafness |
| Bartter syndrome type V• | *CaSR* gene | CaSR | Bartter syndrome with hypocalcemia |
| Gitelman syndrome | *SLC12A3* | NCC (thiazide- sensitive NaCl co-transporter). | Hypomagnesemia, hypocalcuria, growth retardation |

**Table 1 Genetics and presentation of Bartter and Gitelman syndromes**

There are six Bartter syndrome subtypes (I, II, III, IV, IVB, and V) corresponding to six genetic defects.Modified from Seybrerth *et al*[6]. NKCC2: Furosemide-sensitive sodium-potassium-2 chloride cotransporter; ROMK: Renal outer medullary potassium channel; CLC-Kb: Chloride channel Kb; CLC-Ka: Chloride channel Ka; CaSR: Calcium sensing receptor; NCCT: Thiazide-sensitive sodium-chloride cotransporter.

**Table 2 Features differentiating Bartter and Gitelman syndromes**

|  |  |  |
| --- | --- | --- |
| **Features** | **Classic Bartter syndrome** | **Gitelman syndrome** |
| Age at onset | Childhood (early) | Childhood or later |
| Maternal hydramnios | Rare | Absent |
| Polyuria, polydipsia | Present | Rare |
| Dehydration | Often present | Absent |
| Tetany | Rare | Present |
| Growth retardation | Present | Absent |
| Urinary calcium | Normal or high | Low |
| Nephrocalcinosis | Rare | Absent |
| Serum magnesium | Occasionally low | Low |
| Urine prostaglandins (PGE2) | High or normal | Normal |

Modified from Urbanova *et al*[20].