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Chapter 4

Bartter and Gitelman Syndromes

Caius Mihai Breazu, Adrian Bartos and Dana Bartos

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Abstract

Bartter and Gitelman syndromes are rare genetic disorders in which there are specific defects in kidney function, characterized by metabolic alkalosis, hypokalemia, hyperreninemia, and hyperaldosteronism, with or without hypomagnesemia. Blood pressure is normal or low in these patients. Positive diagnosis is one of the exclusions, and the difference between the two syndromes is based on urine calcium levels. Medication has to be taken lifelong. Renal transplantation can correct the transport defect in Bartter and Gitelman syndromes. The symptoms and severity vary from one person to another and can range from mild to severe. Age of onset of overt symptoms can range from before birth to adulthood.

Keywords: Bartter syndrome, genes, mutations, electrolyte imbalances

1. Introduction

Bartter syndrome, originally described by Bartter and colleagues in 1962 [1], represents an autosomal recessive renal tubular disorder characterized by hypokalemia and metabolic alkalosis. In addition, patients have hyperreninemia and hyperplasia of the juxtaglomerular apparatus (the source of renin in the kidney) and secondary hyperaldosteronism [2]. The underlying renal abnormality results in excessive urinary losses of sodium, chloride, and potassium.

2. Etiology

Bartter and Gitelman syndromes are caused by the alteration of a carrier involved in sodium chloride (NaCl) reabsorption. This transporter is located in the thick ascending limb of the loop of Henle in Bartter syndrome and distal convoluted tubule in Gitelman syndrome [3].

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Bartter syndrome subtype	Genetic defect	Clinical syndrome
Type I	SLC12A1 (NKCC2)	Antenatal Bartter syndrome
Type II	KCNJ1 (ROMK)	Antenatal Bartter syndrome
Type III	CLCKB	Classic Bartter syndrome
Type IV	BSND	Antenatal Bartter syndrome with congenital hearing loss
Type IV B	CLCNKA CLCNKB	Antenatal Bartter syndrome with congenital hearing loss
Type V	CaSR	Bartter syndrome with hypocalcaemia
Gitelman syndrome	SLC12A3 (NCCT)	Gitelman syndrome

Table 1. Bartter syndrome subtypes.

Bartter syndrome results from defective transepithelial transport of NaCl in the thick ascending loop or the distal convoluted tubule.

- Transepithelial Cl transport in the thick ascending loop depends on coordinated interplay between the luminal, bumetanide-sensitive, Na-K-2Cl co-transporter (NKCC2), the luminal, K channel (ROMK), the basolateral Cl channel (CIC-Kb), as well as other co-transporters and channels [4].
- Chloride transport in the distal convoluted tubule occurs primarily via the luminal, thiazide-sensitive NaCl co-transporter [4].

There are six subtypes of Bartter syndrome (I, II, III, IV, IVB, and V), each corresponding to a genetic defect (**Table 1**).

Types I through IV—the severity and clinical presentation of Bartter syndrome varies with each type:

- Types I and II are the most severe disorders. They are characterized by polyhydramnios during pregnancy and premature birth. Those who survive infancy develop hypokalemia, metabolic alkalosis, polyuria, and hypercalciuria. Neonates with type II mutations that reduce activity of the renal outer medullary potassium channel (ROMK) often initially develop hyperkalemia [4]. However, as they mature, other potassium channels become active and contribute to the development of hypokalemia. Nephrocalcinosis is common in patients with these mutations and probably contributes to the late development of kidney dysfunction and, rarely, end-stage renal disease [5].
- The classic form of Bartter syndrome, type III, is less severe and presents later in life with hypokalemia, metabolic alkalosis, and hypercalciuria. The reduced severity of type III Bartter syndrome may be due to redundancy of chloride channels in the cells of the thick ascending limb. Loss of ClC-Kb activity causes the disease, but coexistent ClC-Ka activity may ameliorate the process. Some patients with ClC-Kb mutations usually have classic Bartter

syndrome that occurs in infancy or early childhood. It is characterized by hypomagnesemia, hypocalciuria (not hypercalciuria), and unresponsiveness to thiazide rather than loop diuretics [6, 7]. This may be seen because ClC-Kb participates in chloride reabsorption along the distal convoluted tubule and connecting tubule, as well as the thick ascending limb [8]. Many of the mutations that cause Bartter syndrome type III destabilize channel structure, induce ClC-Kb retention within the endoplasmic reticulum, and accelerate channel degradation [6].

- Types IV and IVb have combined defects that involve both the ClC-Ka and ClC-Kb channels and cause severe disease, generally with antenatal presentation and congenital hearing loss. These two chloride channels are critical for normal ion transport in the stria vascularis of the inner ear and are vital to establish normal endocochlear potential differences [9–14]. Because of redundancy of function in the ear, hearing loss requires defects to exist in both ClC-Ka and ClC-Kb. This double defect can occur via at least two mechanisms:
  - As discussed above, the Barttin subunit is an important component of both channels. Thus, a single defect that affects the Barttin subunit reduces the function of both channels (type IV) [9–13]. Hereditary defect in Barttin leads to antenatal Bartter syndrome associated with sensorineural deafness and renal failure.
  - The other mechanism involves double mutations, which reduce the function of both ClC-Ka and ClC-Kb and thereby produce a phenotype similar to the Barttin type IV defect. This is generally called Bartter type IVb [15]. Although some have called this variant "Bartter type V disease," the designation "type V Bartter disease" is most commonly used to describe a gain-of-function mutation in CaSR.
- Type V, usually called autosomal dominant hypocalcemia or autosomal dominant hypoparathyroidism, is due to a gain-of-function mutation in CaSR, encoding the calcium-sensing receptor (CaSR) [16, 17]. In the parathyroid gland, this results in a downward "resetting" of the normal range for serum calcium. As a result, a lower-than-normal serum calcium concentration inhibits parathyroid hormone release, resulting in hypocalcemia.

The tubular defect found in Bartter syndrome is the same as in the chronic ingestion of loop diuretics, while in Gitelman syndrome, it is the same as in the chronic ingestion of thiazide diuretics. In both the syndromes, elevated salt removal will lead to volume depletion and activation of the renin-angiotensin-aldosterone system. The association of secondary hyperaldosteronism with increasing concentration of NaCl at the distal level leads to increased potassium and hydrogen secretion in collecting tubule and distal convoluted tubule, resulting in hypopotassemia and metabolic alkalosis.

The volume depletion explains why patients with Bartter or Gitelman syndrome have lower blood pressure than general population. In addition, in patients with Bartter syndrome, another possible cause of this phenomenon is increased prostaglandin renal clearance with a vasodilator effect [4]. Because urine dilution requires good functioning of the ascending portion of the loop of Henle and the distal convoluted tubule, Bartter and Gitelman syndromes have a low urine dilution capacity [1].

There are also a number of distinct traits between the two syndromes caused by the different site of the NaCl reabsorption abnormality. Thus, patients with Bartter syndrome have a poor

response to the action of loop diuretics, while patients with Gitelman syndrome have a lower response to thiazide diuretics [4].

Calciuresis is normal or increased in Bartter syndrome, similar to loop diuretic effect. On the contrary, calciuresis is low in Gitelman syndrome, as in the use of thiazide diuretics.

3. Prevalence

Gitelman syndrome is a much more common disease than Bartter syndrome [18, 19]. For Gitelman syndrome, a prevalence of 1:40,000 is reported, while Bartter syndrome is less common in the population (1:1,000,000) [18]. The lower prevalence of Bartter syndrome in the population may be due at least in part to prenatal or neonatal death resulting from the disorder before it could be diagnosed [18].

4. Clinical manifestation

Table 2 summarizes the similar and distinct clinical features in Bartter and Gitelman syndromes. In both the syndromes, clinical manifestations are less pronounced in heterozygotes.

Bartter syndrome I, II, IV, and IVB subtypes are most often severe early-onset disease, while subtypes III and V are lighter forms of late-onset disease. However, the correlation between the underlying genetic defect and the clinical phenotype is not absolute.

Subtypes I and II begin antenatally with polyhydramnios and prematurity. Patients who survive infancy develop hypokalemia, metabolic alkalosis, polyuria, and hypercalciuria.

Subtype III is the classic form of Bartter syndrome, starting later than the first subtypes with hypokalemia, metabolic alkalosis, and hypercalciuria. During the course of the disease, this subtype may be associated with proteinuria and renal failure.

Bartter syndrome	Gitelman syndrome
It usually occurs in childhood	It usually occurs in adolescents and adults
Growth retardation present	Growth retardation absent
Normal or low blood pressure	Normal or low blood pressure
Dehydration present	Dehydration absent
Hypokalemic metabolic alkalosis	Hypokalemic metabolic alkalosis
Polyuria and polydipsia present	Polyuria and polydipsia absent
Normocalciuria or hypercalciuria	Hypocalciuria
Maternal polyhydramnios common	Maternal polyhydramnios absent
Normal or slightly low magnesium	Hypomagnesemia

Table 2. Clinical features of Bartter and Gitelman syndromes.

Subtypes IV and IVB usually begin antenatally and should be associated with neurosensory deafness, as the underlying genetic defect affects both NaCl conveying ion channels in the kidney and inner ear.

Subtype V is also known as autosomal-dominant hypocalcaemia or autosomal-dominant hypoparathyroidism. In this case, the underlying genetic defect leads to a "reset" of the normal serum calcium level. Thus, a lower value than normal can inhibit the secretion of parathyroid hormone, leading to hypocalcemia.

5. Differential diagnosis

- Other causes of unexplained hypokalemia and metabolic alkalosis
  - Vomiting/diarrhea
  - Diuretic abuse (**Figure 1**)

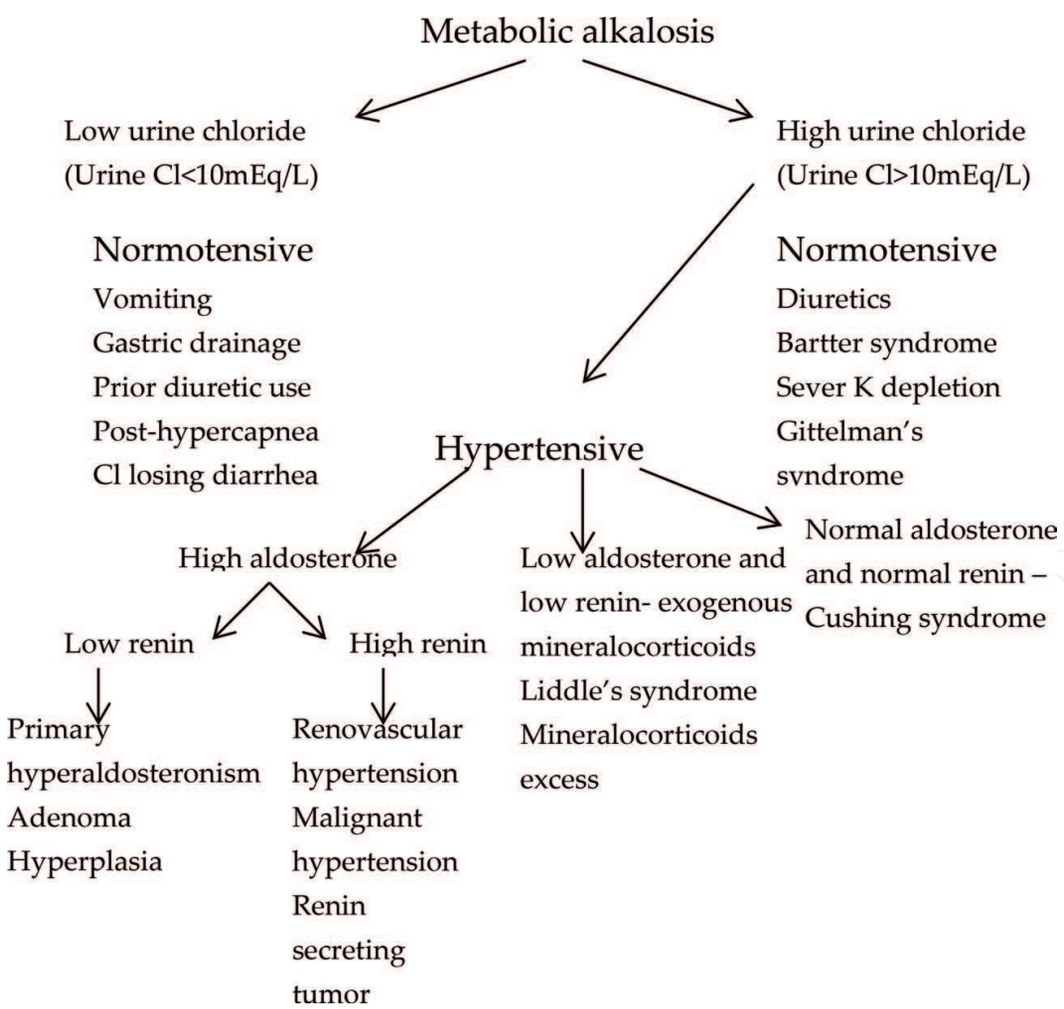

Figure 1. Differential diagnostic of metabolic alkalosis [20].

6. Laboratory studies

- Serum potassium levels—low in all forms of Bartter syndrome
- Serum calcium levels—normal to low
- Serum magnesium levels—low or normal in Bartter syndrome, low in Gitelman syndrome
- Aldosterone levels—elevated
- Urinary potassium levels—elevated
- Urinary aldosterone levels—high
- Urinary chloride levels—high

7. Treatment

The tubular defects in Bartter syndrome cannot be corrected (except by renal transplantation). Thus, treatment is aimed at minimizing the effects of secondary increases in renin, aldosterone, and, in some patients, prostaglandins, as well as correcting the volume deficit and electrolyte abnormalities. There is no consensus on the best treatment for Gitelman syndrome, and magnesium and potassium supplements are usually given.

7.1. NSAIDs and drugs that block distal convoluted tubule sodium-potassium exchange

Nonsteroidal anti-inflammatory drugs (NSAIDs) are an essential component of therapy and can ameliorate many of the abnormalities. The defect in the thick ascending limb of the loop of Henle function in Bartter syndrome often increases renal prostaglandin E2 (PGE2) production. This also occurs with therapeutic loop diuretic use. Markedly increased PGE2 is common in patients with Bartter syndrome types I, II, IV, and IVb.

Indomethacin and celecoxib have been used; there are no clear advantages with either drug [21]. However, careful monitoring is required since NSAIDs can have significant adverse effects including renal and gastrointestinal toxicity.

In addition to an NSAID, a drug that blocks distal convoluted tubule sodium-potassium exchange, such as spironolactone, eplerenone, or amiloride, is usually administered, frequently in higher-than-usual doses (up to 300, 150, and 40 mg/day, respectively). This regimen can raise the serum potassium, reverse the metabolic alkalosis, and partially correct the hypomagnesemia [21, 22]. Among patients with hypokalemia due to potassium wasting of any cause, drugs blocking distal sodium-potassium exchange are typically more effective and better tolerated than potassium supplementation alone.

7.2. Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors reduce the production of angiotensin II and aldosterone and may be a useful adjunctive therapy [23, 24].

Angiotensin receptor blockers (ARBs) should have similar efficacy but have not been well studied in these patients. ACE inhibitors will also reduce proteinuria in these patients when it exists [25].

7.3. Potassium and magnesium supplementation

Most patients require oral potassium and magnesium supplementation since therapy with NSAIDs and drugs that block distal convoluted tubule sodium-potassium exchange is often incompletely effective [26]. However, the restoration of normal serum potassium and magnesium concentrations is often difficult to achieve for one or more of the following reasons:

- Blocking potassium secretion in the cortical collecting tubule with a drug that inhibits sodium-potassium exchange with or without an ACE inhibitor in patients with Bartter syndrome will not reverse the primary defect.
- Hypomagnesemia can contribute to urinary potassium loss.
- When hypokalemia and/or hypomagnesemia are due to urinary wasting, potassium or magnesium supplementation has limited efficacy. As the serum potassium and/or magnesium falls in the untreated patient, the antikaliuretic effect of hypokalemia and the antimagnesiuretic effect of hypomagnesemia gradually reduce potassium and magnesium excretion until a new steady state is attained in which intake and urinary excretion are similar and potassium and magnesium concentrations stabilize at a lower-than-normal level.

The rise in serum concentrations following the administration of potassium and magnesium supplements will reduce the stimulus to potassium and magnesium retention. As a result, most of the administered potassium or magnesium will be excreted in the urine. High doses, which are often difficult to tolerate (e.g., diarrhea with magnesium), are required to achieve a substantial elevation in serum potassium or magnesium. Similar considerations apply to hypokalemia and hypomagnesemia due to other causes of urinary wasting of these cations.

7.4. Renal transplantation

Renal transplantation corrects the transport abnormalities in Gitelman and Bartter syndromes, and recurrent disease in the transplant has not been described. Renal transplantation has been performed in rare patients who developed end-stage renal disease due to coexisting renal disease or the effects of chronic volume depletion, electrolyte abnormalities, drug-related side effects, and/or nephrocalcinosis [27, 28]. In addition, successful preemptive bilateral nephrectomy and renal transplantation have been performed in two patients with severe neonatal Bartter syndrome [28].

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