Understanding Bartter syndrome and Gitelman syndrome

Oliver T. Fremont, James C.M. Chan
Portland, Maine, USA

Background: **We aim to review the clinical features of two renal tubular disorders characterized by sodium and potassium wasting: Bartter syndrome and Gitelman syndrome.**

Data sources: **Selected key references concerning these syndromes were analyzed, together with a PubMed search of the literature from 2000 to 2011.**

Results: **The clinical features common to both conditions and those which are distinct to each syndrome were presented. The new findings on the genetics of the five types of Bartter syndrome and the discrete mutations in Gitelman syndrome were reviewed, together with the diagnostic workup and treatment for each condition.**

Conclusions: **Patients with Bartter syndrome types 1, 2 and 4 present at a younger age than classic Bartter syndrome type 3. They present with sypmtoms, often quite severe in the neonatal period. Patients with classic Bartter syndrome type 3 present later in life and may be sporadically asymptomatic or mildly symptomatic. The severe, steady-state hypokalemia in Bartter syndrome and Gitelman syndrome may abruptly become life-threatening under certain aggravating conditions. Clinicians need to be cognizant of such renal tubular disorders, and promptly treat at-risk patients.**

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Author Affiliations: Tufts University School of Medicine; The Barbara Bush Children's Hospital, Maine Medical Center, Portland, Maine, USA (Fremont OT, Chan JCM)

Corresponding Author: James C. M. Chan, M.D., Professor of Pediatrics, Tufts University School of Medicine; Director of Research, The Barbara Bush Children's Hospital, Maine Medical Center, 22 Bramhall Street, Portland, Maine 04102-3175, USA (Tel: 207-662-2439; Fax: 207-662-6272; Email: cmchanj@comcast.net)

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Review article

Introduction

Bartter syndrome[1,2] and Gitelman syndrome,[3] both result from congenital defects in renal tubular handling of sodium, potassium and chloride.[4,5] We shall highlight the clinical characteristics of each condition[5,6] and comment on the molecular defects[7-10] before discussing diagnostic tests.[11-13] Finally we shall review the impact and limitations of treatment.[14,15] Key references concerning Bartter syndrome and Gitelman syndrome were evaluated in concert with a PubMed literature search from 2001 to 2011. The most current and relevant information from the literature pertaining to these two syndromes were reviewed.

Clinical characteristics common to both syndromes

Patients with Bartter syndrome and Gitelman syndrome present with complaints of constipation, muscle cramps and weakness, secondary to chronic hypokalemia.[16,17] Patients with either syndrome may also present with non-specific dizziness and fatigue. The biochemical features of both syndromes include hypokalemic, hypochloremic metabolic alkalosis associated with high plasma renin activity and high aldosterone concentration.[16-18]

Although the chronic hypokalemia can be mildly symptomatic, it can be aggravated by diarrhea or vomiting, precipitating prolonged QT interval, increased risk of rhabdomyolysis, cardiac arrhythmia, syncope, and sudden death.[19] Alcohol abuse, cocaine or other drug abuse can also precipitate life-threatening arrhythmia.[19] Prompt electrolyte and fluid repair, oral potassium supplementation, potassium sparing diuretics, cyclo-oxygenase inhibitors, and renin-angiotensin blockers become life-saving in such emergencies.[19]

Finally, in familial cases, both conditions are conveyed by autosomal recessive transmission.[18,20]

Clinical characteristics distinct to each syndrome

The site of defect in Bartter syndrome[1,5] is at the thick ascending limb (TAL) of the loop of Henle, whereas

in Gitelman syndrome,[3] the defect resides at the distal convoluted tubule (DCT). Patients with Bartter syndrome present in early childhood and the failure to thrive is more severe and with a great deal of growth retardation.[16,17] Gitelman syndrome is associated with less severe failure to thrive and the growth retardation is milder. Gitelman symptoms are similar to thiazide diuretic-abusers with salt wasting.[21,22]

Sensorineural deafness is a feature of Bartter syndrome type 4, arising from BSND mutation in Bartter syndrome type 4 and digenic mutation of CLCNKA and CLCNKB in Bartter syndrome type 4.[23,24] Hearing defect is absent in Gitelman syndrome, as well as in Bartter syndrome types 1, 2 and 3.

Indeed, Gitelman patients are mostly thought to be asymptomatic. They often present for workup of isolated, asymptomatic hypokalemia,[21] but on closer questioning 80% of Gitelman patients complain of dizziness and fatigue; 70% of the patients complain of muscle weakness and cramps and 50% with nocturia and polyuria, in whom 90% are subsequently found to be salt wasters.

Normal blood pressure in patients with Bartter syndrome[16,17] is a feature thought to be different from the occasional hypotension of Gitelman syndrome. However, there is much overlap in this feature, so that the blood pressure levels cannot be a consistent feature to distinguish between the two syndromes.

Focal segmental glomerulosclerosis[25] has been described in Bartter syndrome. In contrast, Gitelman patients often complain of nocturia and polyuria. Persistent hypokalemia may give rise to interstitial nephritis, signaled by urinary anomalies. Medical non-compliance to potassium chloride supplementation and other therapy is an important issue in long-term follow-up of Bartter and Gitelman patients.

Urinary calcium excretion is important because it distinguishes the two syndromes.[18] In contrast to the hypocalciuria of Gitelman syndrome, Bartter patients are often documented to have hypercalciuria. Patients with antenatal Bartter syndrome (type 1 and type 2) fail to establish an adequate transepithelial voltage gradient to drive calcium and magnesium absorption, giving rise to hypercalciuria and hypermagnesiuria, which increase predisposition to nephrocalcinosis. Patients with type 3 (classic) Bartter syndrome generally do not show nephrocalcinosis and nephrolithiasis.[26,27] In addition, focal segmental glomerulosclerosis was described in the index cases of Bartter syndrome[1] and in the subsequent reports on the performance of kidney biopsies. But, no study of the prevalence of focal segmental glomerulosclerosis in Bartter syndrome has been conducted. Kidney biopsies were not performed in the index cases of Gitelman syndrome.[3] Earlier reports on Bartter syndrome have documented the juxtaglomerular hyperplasia that is thought to be essential to adequately characterize Bartter syndrome.[28] But, more recent reports have not used kidney biopsies to confirm the diagnosis, relying on renal functional tests for that purpose.

Molecular defects

The molecular defects of chloride reabsorption in Bartter syndrome[7-9] and Gitelman syndrome[10] originate at different sites of the nephron. The transport defects for Bartter syndrome are at the TAL of the loop of Henle and for Gitelman syndrome, at the DCT, respectively. Table 1 shows a summary of the gene mutations and gene products in Bartter syndrome and Gitelman syndrome.

Accordingly, Bartter syndrome has been classified into five types (Table).[16-18,29] On the luminal (urinary) side of the TAL cell, the following transport proteins are defective:

Type 1: Na-K-Cl co-transporter protein, previously referred to as antenatal Bartter syndrome or hyperprostaglandin E syndrome.

Type 2: renal outer medullary potassium (ROMK) channel defect often referred to as neonatal Bartter syndrome with transient hyperkalemic metabolic acidosis or as antenatal Bartter syndrome or hyperprostaglandin E syndrome.

On the basal lateral (blood) side of the TAL cell, the following defective transport channels and molecules are seen:

Type 3: mutation in the CLCNKB gene, giving rise to a defective chloride channel Kb (ClC-Kb). Currently the type is referred to as classic Bartter syndrome.

Type 4: BSND gene mutation gives rise to defective function of Barttin, β-subunit of chloride channel Ka (ClC-Ka) and ClC-Kb, required for membrane localization. Digenic inheritance in type 4 Bartter syndrome is outside of the scope of Mendelian inheritance.[23] Type 4 Bartter syndrome has been previously referred to as antenatal Bartter syndrome with sensorineural deafness.

Patients with types 1, 2 and 4 Bartter syndrome have previously been grouped indiscriminately into "hyperprostaglandin E syndrome". Type 5 Bartter syndrome:[29] calcium sensing receptor (CASR) mutation gives rise to a condition characterized by hypocalcemia, suppressed parathyroid hormone function with Bartter-like syndrome. The gene defect occurs on chromosome band 16q13 and the inheritance is autosomal dominant.

Forewarning of Bartter syndrome types 1 and 2 is apparent even during pregnancy with polyhydramnios

Table. Bartter syndrome and Gitelman syndrome: genetic and clinical findings. All patients show hypokalemic metabolic alkalosis, except type 2 Bartter neonates, who initially show transient hyperkalemic metabolic acidosis

	Gene product	Gene mutation	Chromosome band	Inheritance/OMIM	Clinical characteristics
Bartter syndrome (alias)					
Type 1 (antenatal Bartter syndrome; hyperprostaglandin E syndrome)	NKCC2	SLC12A1	15q21.1	AR/601678	Polyhydramnios, prematurity, polyuria, nephrocalcinosis
Type 2 (neonatal Bartter syndrome with transient hyperkalemia; hyperprostaglandin E syndrome)	ROMK	KCNJ1	11q24.3	AR/241200	Polyhydramnios, prematurity, polyuria, nephrocalcinosis, transient hyperkalemic acidosis
Type 3 (classic Bartter syndrome)	ClC-Kb	CLCNKB	1p36.13	AR; many are sporadic/607364	Birth at term, no nephrocalcinosis
Type 4 (antenatal Bartter syndrome; hyperprostaglandin E syndrome with sensorineural deafness, BART)	Barttin (b-subunit of ClC-Ka and ClC-Kb)	BSND	1q32.3	AR/602522; digenic in CLCNKA and CLCNKB genes	Prematurity, sensorineural deafness, no nephrocalcinosis
Type 5 (hypocalcemia with Bartter-like syndrome)	CASR	L125P	3q21.1	AD/601199	Hypocalcemia, suppressed PTH
Gitelman syndrome	NCCT	SLC12A3	16q13	AR/263800	Hypocalciuria, hypermagnesiuria and hypomagnesemia

NKCC2: furosemide-sensitive Na-K-Cl cotransporter; ROMK: renal outer medullary K channel; ClC-Kb: chloride channel-Kb; ClC-Ka: chloride channel-Ka; CASR: calcium-sensing receptor; NCCT: thiazide-sensitive NaCl cotransporter; AR: autosomal recessive; AD: autosomal dominant; OMIM: Online Mendelian Inheritance in Man; PTH: parathyroid hormone.

and becomes more pressing in the neonate with marked polyuria and significant dehydration episodes.[14] Hypercalciuria of types 1 and 2 Bartter syndrome patients leads to nephrocalcinosis, which is not present generally in type 3 or type 4 Bartter syndrome patients. The initial, neonatal presentation of Bartter syndrome type 2 is hyperkalemic, metabolic acidosis.[30] Such symptoms overlap those of pseudohypoaldosteronism, and type 4 Bartter syndrome patients have often been misdiagnosed as having pseudohypoaldosteronism. Steadily, as ROMK and other potassium channels or transporters recompense, these neonates become hypokalemic and show metabolic alkalosis. Once these more typical Bartter-like features come to the fore, the physician usually will arrive at the correct diagnosis.

Type 3 Bartter syndrome patients have the mildest presentation, presumably although CLCNKB is mutated in type 3 Bartter syndrome, CLCNKA chloride permeability is preserved.[30] In view of the fact that CLCNKA is also present in the DCT, the symptoms of Bartter syndrome and Gitelman syndrome overlap.

The presentation of type 4 Bartter syndrome is more severe, because both CLCNKA and CLCNKB channels are affected.[30] Type 4 Bartter syndrome has an altered subunit protein, barttin, which is needed for potassium chloride membrane localization. Different mutations of CLCNKA lead to different functional deficits in barttin, resulting in different severity of type 4 Bartter syndrome.[23]

Hypocalcemia with Bartter-like syndrome (alias type 5 Bartter syndrome) results from autosomal dominant, L125P mutations of an extracellular basolateral CASR, giving rise to hypocalcemic hypercalciuria and suppressed parathyroid hormone activity.[29,30] Bartter syndrome type 5 is the only TAL salt-losing defect, which is inherited by autosomal dominant transmission. All other types of Bartter syndrome are autosomal recessive.

Gitelman syndrome[31] is due to defective NaCl-cotransporter (NCCT) at the DCT, encoded by the SLC12A3 gene.

Significantly, the abnormal mutation of the NCCT protein in DCT is also expressed in blood mononuclear cells,[31] which are easily accessible. Thus, the confirmation of NCCT protein mutation in the blood mononuclear cells becomes a useful tool in diagnosis of Gitelman syndrome.

Aside from providing diagnostic tools and better classification of Bartter-like syndromes,[4] how does research into the molecular mechanisms of these rare, congenital tubular diseases translate to the patient? Recent reports on the SPAK and OSRI molecules in Bartter syndrome, Gitelman syndrome and pseudohypoaldosteronism type II (PHA II) stimulate a lot of interest.[32,33] SPAK stands for [STE20/SPS1-related proline/alanine-rich kinase]. It is activated by WNK1/4, which can in turn phosphorylate and activate NCCT/NKCC1/2. Oxidative stress-responsive kinase-1 is abbreviated to OSR1. There is enormous interest concerning how these two kinases[33] enter

blood pressure control, in these rare, congenital renal diseases—not only in gaining insight into basic mechanism of blood pressure regulation, but exciting potentials in finding a significant, new class of anti-hypertensive medication.

The molecular mechanism of childhood deafness has everything to do with potassium and chloride pumps.[34] Cochlear hearing function relies on a number of molecular processes. Hearing requires inflow of potassium into hair cells of the cochlear. Potassium is driven into hair cells by electro-chemical forces and recycled via KCNQ4 channels or enters Deiter's cells (via KCC3, KCC4). Potassium chloride from hair cells passes through connexins, returns or secrets into endolymph at the cochlear.[34] Disturbances in transport, return or secretion of potassium chloride are the molecular basis of childhood deafness, and likely apply to the sensorineural deafness in type 4 Bartter syndrome.

Diagnosis

The differential diagnosis of hypokalemic, metabolic alkalosis include vomiting in young infants, especially that related to pyloric stenosis, chloride-losing diarrhea, cystic fibrosis, and diuretic abuse. Ongoing vomiting or diarrhea is usually clear from the history. Measurement of urinary chloride excretion can help distinguish between renal and non-renal causes of chloride loss.[13] It can be difficult to distinguish between diuretic abuse and Bartter or Gitelman syndromes without directly evaluating the urine for presence of diuretics.

Distinguishing between Bartter and Gitelman syndromes is not always straightforward due to phenotypic variance. Genetic diagnosis is now possible, but there are several limitations including lack of general availability, cost, and absence of "hot spot" mutations along the gene. As mentioned, Bartter syndrome is typically associated with hypercalciuria and Gitelman syndrome with hypocalciuria, although some patients with type 3 Bartter syndrome have normal urinary calcium excretion.

A thiazide test has recently been described to help distinguish between the two conditions.[11] It involves oral administration of hydrochlorothiazide (1 mg/kg up to 50 mg), after a 7-day "washout" period, during which therapies aside from potassium and magnesium supplements are held. In patients with Gitelman syndrome, where the defect is in the thiazide-sensitive NCCT, this results in very little change (<2.3%) in the fractional excretion of chloride from baseline. In patients with Bartter syndrome, however, this blunted response is not seen.[11,12] This test is not recommended for infants or children at age of less than 7 years, with suspected Bartter syndrome because of a higher risk of volume depletion.

Management

Acute therapy in settings such as dehydration in a young patient with neonatal Bartter syndrome, cardiac arrhythmia, or rhabdomyolysis due to hypokalemia[19] is beyond the scope of this review. The focus of chronic therapy in patients with Bartter syndrome and Gitelman syndrome includes electrolyte replacement as well as inhibition of secondary increases in prostaglandin production and/or the renin-angiotensin-aldosterone axis, which exacerbate the urinary electrolyte losses.

Bartter syndrome is typically treated with indomethacin and potassium chloride. The dose of indomethacin can be as high as 2-3 mg/kg per day (mean: 2.1 mg/kg per day in one study).[15] Indomethacin can lead to improvement in laboratory parameters as well as the failure to thrive typically seen in patients with Bartter syndrome. Indomethacin should be used with caution in premature infants because of the increased risk for gastrointestinal perforation or necrotizing enterocolitis.[35,36] Long-term gastrointestinal side effects of indomethacin including chronic gastritis and gastric ulcers can be dose limited, and cyclooxygenase-2 selective inhibitors might be considered as an alternative.[37]

Sodium chloride supplementation may be needed early in life, but high dietary salt intake is often sufficient in older children. Other medications to consider, depending on clinical and laboratory parameters, include ACE inhibitors, potassium-sparing diuretics (particularly spironolactone), and magnesium supplementation. Thiazide diuretic should not be used to treat hypercalciuria and nephrocalcinosis in Bartter syndrome patients because further inhibition of salt reabsorption in the DCT removes the kidneys' ability to compensate, while increasing the risk of significant dehydration.

Because patients with Gitelman syndrome do not typically show the increased prostaglandin production seen in patients with Bartter syndrome,[37] the same response to indomethacin is not seen. Hypomagnesemia is a more prominent component of Gitelman syndrome, so magnesium supplementation is routinely required. Otherwise management of Gitelman syndrome is similar to that of Bartter syndrome.

Questions for the future

Long-term outcome study of over 10 years in type 1 and

type 2 Bartter syndrome patients showed a glomerular filtration rate of less than 90 mL/min per 1.73 m^2 in 25% of the patients.[14] This is likely the result of the prevalent nephrocalcinosis. In addition, interstitial nephritis from life-long hypokalemia or non-steroidal anti-inflammatory medications may be compounding factors. The use of indomethacin at an average dose of 0.9 mg/kg body weight per day for over 10 years is unrelated to any lesions on kidney biopsies in patients with type 1 and type 2 Bartter syndrome.[14] Finally, almost 9% of patients with these two types of Bartter syndrome are found to have gallstone.[14] Predisposing factors include prematurity, chronic use of loop diuretics and dysfunction of hepatobiliary ROMK.

Some experts regard hypocalcemia with Bartter-like syndrome from CASR (OMIM 601199) as type 5 Bartter syndrome.[29] Others list antenatal Bartter syndrome from CLCNKA and CLCNKB mutations as type 5 Bartter syndrome.[4] Out of such confusion, a proposal has been made of a new classification,[4] utilizing the advances in our understanding of the syndrome.

Conclusion

Chronic hypokalemia in patients with Bartter syndrome and Gitelman syndrome can be aggravated by diarrhea or vomiting into life-threatening rhabdomyolysis, cardiac arrhythmia, and syncope. Clinicians need to be cognizant with these congenital, renal tubular disorders, and promptly treat such patients. Finally, these syndromes of normal (or low) blood pressure, despite hyperreninemia and hyperaldosteronism, may provide insight into molecular control of blood pressure and lead to new antihypertensives.

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