Bartter syndrome

Author: Dr Giacomo Colussi[1]
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[1]A.O. Ospedale di Circolo e Fondazione Macchi, Viale Borri, 57, 21100 Varese, Italy.
Giacomo.Colussi@ospedale.varese.it:

Abstract
*Bartter syndrome (BS) is a hereditary condition transmitted as an autosomal recessive (Bartter type 1 to 4) or dominant trait (Bartter type 5). The disease associates hypokalemic alkalosis with varying degrees of hypercalciuria. It is a consequence of abnormal function of the kidneys, which become unable to properly regulate the volume and composition of body fluids due to defective reabsorption of NaCl in a specific structure of the kidney called the " loop of Henle ". A first consequence of the tubular defect in BS is polyuria. Indeed, high urine volume is already present during fetal life, and is responsible for particular complications of pregnancy, i.e. polyhydramnios and premature delivery. Low potassium levels in the blood may result from overactivity of the renin-angiotensin II-aldosterone hormone system that is essential in controlling blood pressure. To date, at least five genes have been linked to BS, and characterize five types of BS. BS type 1 is linked to mutations of the gene SLC12A1 (*Solute carrier family 12 sodium/potassium/chloride transporters, member 1) *on chromosome 15 (15q15-q21.1). BS type 2 is linked to a gene called KCNJ1 (mapped to chromosome 11q21-25), BS type 3 is linked to the gene ClCNKb (mapped to chromosome 1p36) while BS type 4 is linked to gene BSND (mapped to chromosome 1p31). BS type 5 is associated with activating mutations of the CASR gene (mapped to chromosome 3q13.3-q21). Patients with BS are usually symptomatic early in life (occasional patients with BS type 3 or type 4 may even reach adulthood with few if any manifestations), growth is usually below the age standards and final height may also be compromised. At present, BS cannot currently be cured, and treatment is mainly directed at correcting electrolyte disturbances, i.e. hypokalemia and possibly hypomagnesemia.*

Keywords
Bartter syndrome, diuretic abuse, hypokalemia, hyperreninemia, hyperaldosteronism (secondary, hyperreninemic), hypercalciuria, hypomagnesemia, metabolic alkalosis (hypokalemic), nephrocalcinosis.

Disease name and synonyms

Bartter syndrome (BS), hypokalemic alkalosis with hypercalciuria, hyperprostaglandin E syndrome (HPS), antenatal Bartter syndrome (aBS), infantile Bartter syndrome, furosemide-like salt-losing tubulopathy, autosomal dominant hypocalcemia with Bartter syndrome.

Excluded diseases

Gitelman syndrome (hypocalciuric variant of Bartter syndrome)

Pseudo-Bartter syndrome (diuretic abuse, surreptitious vomiting)

Definition

BS is a consequence of abnormal function of the kidneys, which become unable to properly regulate the volume and composition of body fluids. More specifically, the genetic defect of BS impairs the function of a specific structure of the kidney, called loop of Henle, which reabsorbs a consistent fraction (about 30%) of fluids and electrolytes produced by glomerular blood filtration. Mutations of several genes may result in BS, which is a genetically heterogeneous condition (Bettinelli *et al.*, 1998; Kamel *et al.*, 2002; Reinalter *et al.*, 2004).

Differential diagnosis

The main differential diagnosis is with Gitelman syndrome, also known as the hypocalciuric variant of BS. Chronic intake of loop-acting or thiazide diuretics also induces a biochemical profile almost indistinguishable from BS; it may occur in persons who, for psychological reasons, deny taking any drugs, thereby making the diagnosis difficult (Colussi *et al.*, 1992). Though almost invariably the latter occurs in adults, I have seen a case of surreptitious diuretic abuse in a 12-year-old adolescent girl who stole the pills from her mother, who also abused of diuretics. Self-induced vomiting in persons suffering from anorexic-bulimic disorder may also generate a biochemical profile similar to that of BS. A large group of disorders with primary overproduction or defect of a mineralocorticoid hormone may present with hypokalemic alkalosis but, unlike BS, they have low renin levels and high blood pressure. From early infancy to childhood, BS must be considered in the differential diagnosis of genetic conditions predisposing to dehydration and failure to thrive, such as nephrogenic diabetes insipidus, cystic fibrosis, pseudohypoaldosteronism, congenital adrenal hyperplasia, however the biochemical profile usually enables easy differentiation.

Clinical description and mechanism

Among the several functions of the kidney, a vital one is the regulation of the composition and volume of body fluids, by "filtering" the blood at specialized structures, called glomeruli, and reabsorbing the essential constituents from the filtered fluid along a tubular structure (the renal tubule) which drains every glomerulus. About 120-160 litres of fluid flow through the glomeruli along the renal tubules every day for an adult of average body weight (i.e. 1.5-2 litres every Kg of body weight), and only about 1 litre remains in final urine as the solvent for body waste. Discrete segments of the renal tubule perform specialized functions; when any of these functions is not properly performed, several severe consequences may follow, as exemplified by BS.

In BS, the genetic defect impairs the function of some specialized proteins, which reabsorb sodium and chloride in a specific site in the renal tubule, the loop of Henle. Reabsorption of other ions, such as potassium, calcium, magnesium (Mg) and of water may also be, directly or indirectly, affected. Since substantial amounts of Na and Cl are normally reabsorbed in the loop of Henle every day (about 30% of the amount filtered), the consequences of this defective reabsorption are usually severe. However, the extent of the defect may vary from one patient to another (from minor to complete abolition of protein function), and clinical severity may thus vary in BS, "mild" and "severe" cases being possible.

A first consequence of the tubule defect in BS is increased urine volume, which results in classical symptoms, such as polyuria (abundant and frequent micturitions), nocturia (the necessity to get up, sometimes several times, to void during the night) and, frequently nocturnal enuresis (*i.e.* bed-wetting) until late childhood or even adolescence. Since they lose so much water, BS patients are polydipsic. These symptoms are usually pronounced in BS. Indeed, high urine volume is already present during foetal life, and results in particular complications of pregnancy, *i.e.* polyhydramnios (increased volume of amniotic fluid) and premature delivery, usually of small gestational age babies. In the early months or years of life, unrecognized dehydration may occur, manifested by vomiting, fever, feeding problems and failure to thrive persisting until late adolescence.

Because the main functions of Na and Cl in blood is to control the volume of fluids in interstitial spaces and blood, another characteristic of BS is low volume of intravascular fluids, resulting in low blood pressure. Although blood pressure is rarely so low as to induce major discomfort, at least part of the fatigue that most of the patients complain of, especially in hot climates, may be related to low blood pressure. A specific consequence of the low intravascular volume is the increase, sometimes to extremely high blood levels, of renin and aldosterone: the renin-angiotensin II aldosterone hormone system acts to prevent dangerous declines of blood pressure and volume by increasing vascular resistance and fluid reabsorption in still properly functioning renal tubules. Thus, compensatory mechanisms (within and outside the kidney) counteract the tubule defect, thereby maintaining body fluid balance at new levels, still compatible with life.

Increased renin secretion in BS occurs within the kidney itself, in a specialised structure called *juxtaglomerular apparatus*; this apparatus was shown to undergo extreme hypertrophy since the first descriptions of BS. Besides reduced intravascular volume, a main stimulus to renin secretion in BS is increased renal production of

prostaglandin E, which has been shown to be associated with inhibition (both from genetic mutation or pharmacological effect of diuretics) of all the solute carriers associated with BS. Increased plasma levels of prostaglandin E in BS have also been considered responsible, in full or in part, for extrarenal symptoms, such as fever, vomiting, diarrhoea, failure to thrive, osteopenia and growth retardation.

Plasma Na and Cl are usually maintained at normal, or near normal, level by potent homeostatic mechanisms, so that the most notable electrolyte abnormality that frequently leads to the discovery of BS is hypokalemia (*i.e.* low blood K levels). However, in most severe forms (the so called antenatal BS), severe dehydration may be associated with both hyponatremia and hypochloremia. In babies with the so called BS type 2 (see "etiology"), in which a potassium channel function (the so called ROMK protein) is abnormal, there may be hyperkalemia early in life, to be followed later on by classical hypokalemia as long as renal tubule undergoes post-natal "maturation". In BS, hypokalemia itself is only in small part due to the basic reabsorption defect but is mostly a consequence of compensatory mechanisms activated to reabsorb more Na and Cl downstream from the site of the defect at the expense of K wasting. A similar mechanism explains the high blood levels of the bicarbonate anion (resulting in increased blood alkalinity, or metabolic alkalosis). Some patients also lose Mg in their urine, with subsequent hypomagnesemia observed in approximately 10% of BS patients. The consequences of all these electrolyte abnormalities may vary widely in different patients, from very severe to extremely mild, depending on the genetic basis of the disorder. Since K and Mg are important for muscle and cell function, the most common complaints related to hypokalemia include chronic fatigue, almost universal in severely hypokalemic patients, and decreased muscular strength, which may progress to complete paralysis in association with conditions which further reduce blood K levels, such as vomiting and diarrhea. Patients with known hypokalemia should avoid strenuous muscular exercises, because of the risk of muscular fibre rupture (so called rhabdomyolysis).

In most severe forms of BS (for which different terms have so far been used: "antenatal" BS, "neonatal" BS, "infantile" BS, and hyperprostaglandin E syndrome; all are usually caused by mutations of NKCC2 and ROMK carriers, see below), chronic dehydration, and possibly high prostaglandin E levels, are associated with varying degrees of growth retardation, failure to thrive, fever and vomiting.

The loss of calcium in urines (*i.e.* hypercalciuria) predisposes BS patients to calcification of the renal tissue (so called nephrocalcinosis), which may occur in the very first months of life; this is observed in BS types 1 and 2, but usually not in type 4 and only rarely in BS type 3 (see below).

Plasma Ca levels are normal in BS, with the exception of rare patients with a newly described syndrome (BS type 5, due to activating mutations of the membrane receptor for Ca ions, see below), characterized by hypocalcemia and very low parathyroid hormone (PTH) levels, in addition to the usual biochemical profile of hypokalemia, alkalosis and hyperreninemia (Watanabe *et al.*, 2002).

Other than the tubule defect, renal function usually remains normal in patients with BS and they generally do not require dialysis; chronic dehydration and nephrocalcinosis, however, may lead to some degree of renal insufficiency.

Hearing defect is a specific symptom of BS type 4 (caused by mutations of "Barttin" protein, which is expressed both in the kidney and in the cochlea and is necessary for the sensory-neural transduction of sounds) (Miyamura *et al.*, 2003; Reinalter at al., 2004).

Most BS patients are usually symptomatic early in life, although occasional patients (mostly BS type 3 and rare patients with BS type 4 and 5) may continue into adulthood with few if any manifestations (Zelikovic *et al.*, 2003; Watanabe *et al.*, 2002).

Table 1 summarises the main clinical and phenotypical aspects of BS in relation to specific genetic mutations involved (see "etiology").

Management including treatment

At present, BS cannot be cured, and treatment is mainly directed at correcting dehydration and electrolyte disturbances, *i.e.* hypokalemia and possibly hypomagnesemia. The latter disorder might not require any treatment. Simply increasing the intake of single electrolytes has little benefit, since urinary excretion increases proportionally. Even increasing of dietary salt intake, which would appear logical, may in fact result in deleterious effects, since it enhances urinary K excretion. Patients with the less severe forms of BS can maintain salt balance even at moderately low intake, it is thus preferable to reduce rather than increase dietary salt intake, thereby making satisfactory control of blood K levels easier. The situation may be different in infants, since their kidneys have not yet developed maximal reabsorptive capacity; they need appropriately adapted supplementation of fluids and electrolytes. Adult patients with blood K levels above 3 mmol/L may not need any supplementation, while patients with much lower values are usually given oral K supplements; the use of special "K-sparing" diuretics has proved useful in some BS patients. Other commonly used drugs are the so-called non-steroidal anti-inflammatory drugs, due to their antiprostaglandin effect; they are the first-choice

drugs in patients with early-onset symptoms (the so called “antenatal” BS, or “hyperprostaglandin E” syndrome; this kind of presentation occurs usuallly in BS type 1, 2 and 4, according to the gene mutation terminology, see below). Side effects of antiprostaglandin drugs may be common, accounting for reduced compliance in the long term. Drugs, which block the effects of renin and angiotensin II (so called angiotensin-converting enzyme ACE-inhibitors and sartans) have also been tested, but compliance is usually poor because of their blood pressure-lowering effect in these patients with already low blood pressure. Lastly, it should be kept in mind that, in stress situations (general diseases, surgical procedures, trauma) blood electrolyte levels may change rapidly, requiring prompt and vigorous intravenous treatment.

Etiology

BS is a hereditary disease, with an autosomal recessive (BS type 1 to 4) or autosomal dominant (BS type 5) mode of transmission. Genetic research conducted over the last 15 years has led to the discovery and sequencing of 5 genes linked to BS. Thus, appropriate genetic tests can now be performed to obtain a specific diagnosis and, theoretically, also to screen for healthy carriers. However these tests are complex, time-consuming and costly, and consequently, they are still mostly reserved for research purposes.

To date, at least five genes have been linked to BS, and characterize five types of BS (Bettinelli *et al.*, 1998; Watanabe *et al.*, 2002; Konrad *et al.*, 2000; Reinalter *et al.*, 2004). BS type 1 is linked to mutations of the *SLC12A1* gene on chromosome 15 (15q15-q21); its product is a protein (NKCC2 or BSC) highly homologous with NCCT/TSC (*i.e.* the solute carrier which is mutated in another tubular disorder, Gitelman syndrome). BSC reabsorbs Na, Cl and K in the Henle's loop and is the target of the so-called loop-acting diuretics, such as furosemide. BS type 2 is linked to a gene called *KCNJ1* (mapped to chromosome 11q21-25) while BS type 3 is linked to the *ClCNKb* gene (mapped to chromosome 1p36). The products of these last two genes are proteins (ROMK and ClCN-Kb respectively), which constitute special "channels" (for K and Cl, respectively) necessary for proper electrolyte reabsorption by the cells in Henle’s loop. The abnormal function of any of these proteins results in similar final effects. The fourth gene responsible for BS type 4, *BSND*, encodes a protein product called Barttin, which is a β-subunit of the Cl-channel encoded by the BS type 3 gene, *i.e*. ClCN-Kb. Its mutations impair the Cl-channel function as in BS type 3. The fifth gene, linked to BS type 5, is *CASR* (mapped to chromosome 3q13.3-q21) whose product is the cell-membrane Ca-sensing receptor (CaR). Activating mutations of this protein are first associated with a condition called familial autosomal dominant hypocalcemia (ADH); CaR activating mutations increase the sensitivity of parathyroid gland cells to blood Ca levels, and cause a decrease of PTH secretion despite low plasma Ca levels. In renal tubular cells located in the “thick” portion of the ascending limb of the loop of Henle, CaR activation reduces reabsorption of Ca and Mg. In rare patients for whom the mutation is associated with very high “gain of function”, maximal stimulation of this receptor by blood Ca levels also results in the inhibition of the reabsorption of Na and Cl, mostly due to inhibition of the ROMK channel. Thus, the same events occur as in BS type 2. The symptoms are basically related to hypocalcemia, and fluid and electrolyte abnormalities are detected only at the biochemical work-up for the Ca disorder. The terms autosomal dominant hypocalcemia with Bartter syndrome, or BS type 5 have both been proposed for this disorder (Hebert, 2003).

Clinically, BS type 3 and 5 appear to be less severe than types 1 and 2, despite similar biochemical indices (Zelikovic *et al.*, 2003). A specific feature of BS type 4 is congenital sensorineural deafness. BS types 1 and 2 account for most cases of the so-called “antenatal”, or “infantile” BS, a particularly severe form of BS.

Many mutations have been detected in each of the 5 genes, with effects on proteins ranging from slight compositional and functional changes to complete deletion.

Other still unknown genes are likely to be associated with BS, since at least 10% of patients with clinical symptoms of BS have no detectable mutations in the 5 genes cited above. Active research is still needed in this field.

Genetic counselling

The parents of an affected child might wish to know the risk of BS in any future pregnancy. Because BS (types 1 to 4) is an autosomal recessive hereditary disorder, the risk is 25% (*i.e.* 1 in 4 for each conception). The parents are usually heterozygous, asymptomatic carriers of specific gene mutations. To date, no biochemical abnormalities have been reported in heterozygous individuals. Therefore, the presence of a single unmutated allele of each transporter gene seems sufficient for good functionality of tubule cells. Asymptomatic brothers and sisters of an affected individual will either be heterozygous carriers (50% probability) or unaffected (*i.e.* both their alleles are unmutated, 25% probability).

A special situation might be the case of BS type 3, since this disorder may have a highly variable phenotype (from severe "antenatal" forms to almost asymptomatic patients diagnosed during adolescence or adulthood), it might be wise to screen both parents for a mild form of the disease

(a simple determination of plasma K levels is a sensitive and low-cost screen test). If one of the parents is shown to be affected, the chance of transmitting the disease in any future pregnancy will be 50% (*i.e.* 1 out of 2).
If a patient with proven BS is concerned about the risk of transmitting the disease to future offspring, assuming that his/her partner is healthy, all their children will be healthy carriers; the partner's genotype is crucial, because if he/she happens to be a healthy carrier, there is 50% of each child to be affected. BS represents a good example of how genetic testing (of the patient to define the gene involved, and of the partner to rule out heterozygous mutations of the same gene) may be particularly useful for genetic counselling. In the very hypothetical case that 2 affected individuals would like to know the risk of disease in their offspring, the answer is by no means easy: if both the patients have the same type of BS, all the children will be affected; however if the parents have different types of BS, e.g. type 1 and 2, or type 2 and 3 (or 4), or type 1 and 3 (or 4), all the children will be double heterozygotes. To date, no such event has been described, but it is highly likely that these double heterozygotes will be completely asymptomatic, since each parent will transmit only one mutated allele of 2 different genes.
As for BS type 5, disease transmission occurs from an affected parent to his child, with a 50% probability in each pregnancy.

Antenatal diagnosis
Antenatal diagnosis of BS was made for a child with *ROMK* mutations and BS type 2 by genetic testing of amniocytes at the 26th week of gestation. The diagnosis allowed better management of the pregnancy (by administering an antiprostaglandin drug to the mother, which prevented the progression of polyhydramnios). Treatment of the newborn should also be initiated at birth. Diagnostic testing of amniocytes might be indicated for mothers of affected children, or potential heterozygous carriers (close relatives of affected persons).

Unresolved questions
Because at least 10% of patients with clinical symptoms of BS do not have any mutations of known genes, active research is still needed to clarify both the mechanisms of the disease in these patients and the physiology of solute reabsorption in Henle's loop.

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Table 1. Clinical and phenotypical characteristics in patients with different BS type caused by mutations of specific genes

	Bartter Syndrome				
	Type 1	Type 2	Type 3	Type 4	Type 5
Gene name	*SLC12A1*	*KCNJ1*	*CLCNKB*	*BSND*	*CASR*
Protein name	NKCC2	ROMK	ClCN-Kb	Barttin	CaR
Major symptoms	Polyuria/ Dehydration/ Growth retardation	As for type 1	Variable (from mild to severe)	As for type 1 + deafness	Hypocalcemia Seizures
"Antenatal" phenotype	++±	+++	±	++±	-
Nephrocalcinosis	++±	+++	±	-	+++