EDUCATIONAL ARTICLE

Bartter's syndrome

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Abstract
Bartter's syndrome (BS) is an autosomal recessive disorder characterized by hypokalemic, hypochloremic metabolic alkalosis with normal or low blood pressure despite high plasma renin activity and serum aldosterone. It has been classified into different types based on its different phenotypic presentation and genetic etiology.

Introduction
Bartter's syndrome (BS) is a group of inherited salt losing tubulopathies presenting as metabolic alkalosis with normotensive hyperreninemia and hyperaldosteronism. The inheritance pattern is autosomal recessive. Since Fredric Bartter and his colleagues first described these features in two children and a man in 1962, many advances have occurred in better understanding the genetics, pathophysiology, clinical features and management of the disease.(1)

Classification
Depending on the severity and age of presentation BS can be classified as
1. Antenatal Bartter syndrome
2. Classical Bartter's syndrome.

Antenatal BS is characterized by in utero or neonatal age of presentation, presence of nephrocalcinosis, higher urinary loss of sodium, potassium and chloride compared to that in classical BS

Based on pathophysiology and genetics B.S. can be classified as (Table1) (2):

1. Antenatal BS type I, involving defect in NaK2Cl cotransporter in thick ascending limb (TAL) because of mutation in SLC12A1 gene on 15q15-21 chromosome.
2. Antenatal BS type II, involving defect in ROMK (Renal Outer Medullary Potassium Channel) in TAL and collecting duct (CD) because of mutation in KCNJ1 gene on chromosome 11q24.
3. Classic BS type III, involving defect in CIC-Kb channel in TAL and distal convoluted tubule (DCT) because of mutation in CLCNKB gene on chromosome 1p36.
4. BS type IV, Bartter's syndrome with sensorineural deafness (BSND) variant occurs because of mutation in the BSND gene on chromosome 1p31 coding for protein "Barttin" which forms ß subunit of CICKb and CICKa channel located on basolateral membrane of TAL and inner ear epithelium.
5. Gitelman's or hypomagnesemic variant involving defect in NCCT channels in distal tubule because of mutation in SLC12A3 gene on chromosome 16q13.
6. Pseudo-Bartter's syndrome.

Antenatal Bartter's Syndrome:
Signs and symptoms of antenatal or neonatal B.S. may be present or identifiable in utero. Antenatally there is history of unexplained polyhydramnios with premature delivery. Biochemical abnormality of amniotic fluid with normal sodium, potassium and prostaglandin levels with constantly elevated chloride levels have been documented (3).

Phenotypic features like triangular facies characterized by prominent forehead, large eyes, strabismus, protruding ears and drooping mouth have been reported (4). After birth symptoms occur in first week of life in the form of polyuria, lethargy, poor feeding and rapid weight loss. Urine output may increase upto 10ml/kg/day. Hematological investigations show hyponatremia, hypokalemia, hypochloremia with metabolic alkalosis. Polyuria with urine of low specific gravity i.e. hyposthenuria occurs. There is increased urinary loss of sodium, chloride, potassium and prostaglandin. Hypercalciuria with nephrocalcinosis is found mainly in type I, II and BSND variant of BS. Levels of renin, aldosterone and prostaglandin E2 in blood are high and important in establishing the diagnosis. In past various mechanisms like juxtaglomerular hyperplasia, insensitivity to angiotensin II, primary hypersecretion of prostaglandins etc. were proposed to explain the pathophysiology of BS. But all these mechanisms have now been overruled. The basic defects in tubular channels as mentioned above causes increased loss of salts in urine, which leads to activation of renin-angiotensin-aldosterone axis leading to hyperaldosteronism and hyperreninemia. The exact mechanism of increased prostaglandin level in blood and urine is still not known but it appears to be secondary to underlying defect in the transport of sodium chloride in thick ascending limb. So the term "Hyperprostaglandin E syndrome" which was previously used for these tubulopathies will be a misnomer, as increased prostaglandin level is a secondary phenomenon. But why these patients with high renin, aldosterone levels have normal blood pressure? The mechanism still remains unexplained whether it is really due to unresponsiveness of blood vessels to angiotensin II or not!

BSND Variant:
BSND variant was originally described in children born to consanguineous couples from Bedouin family of Southern Israel. There were reports of sensorineural deafness and chronic renal insufficiency due to tubulointerstitial fibrosis in these patients. Renal function deterioration was later proved to be inconsistent finding. This variant also presents antenatally with polyhydramnios in mother and premature delivery. The BSND gene responsible for this variant has been mapped on chromosome 1p31 coding for a protein named barttin, which forms the beta subunit of basolateral chloride channel in distal tubule including CICkb. These channels also contribute to endolymph secretion in inner ear. Karl et al have reported a case with digenic mutation in CIC-Ka and CIC-Kb channels presenting as BSND variant.
Postnatally they present with polyuria and they have high chances of neonatal infection compared to their degree of prematurity (5). Other features and investigation findings are similar to type I and II antenatal BS.

Classical Bartter's Syndrome:

as compared to antenatal BS. Classical BS presents in childhood with failure to thrive. They also have polyuria, polydipsia, vomiting, constipation, salt craving leading to dehydration. History of polyhydramnios and premature delivery is generally absent. Urinary calcium is either normal or slightly elevated and these patients have very low chances of nephrocalcinosis. The biochemical abnormality is related to a defect in Cl^- transport in thick ascending limb of Henle including CIC-Kb channel. But in some patients with classical BS no abnormalities could be identified.

Gitelman's Syndrome:
It also has milder course and later age of onset (6-13 yrs). Patients present with fatigue, muscle weakness and recurrent episodes of tetany in the form of carpopedal spasm. They don't have history of polyhydramnios and premature birth. What distinguishes them from BS is the presence of hypomagnesemia & hypocalciuria instead of hypercalciuria, the reason for which is not clear. Hypomagnesemia is probably due magnesium wasting in distal convoluted tubule due to inhibition of magnesium uptake in presence of hypokalemia.

Pseudobartter's Syndrome:
These include group of condition in which there is hypokalemic metabolic alkalosis with no pathology in renal tubules hence the name "Pseudobartter's Syndrome". Such conditions include cystic fibrosis, surreptitious diuretic use, chronic administration of chloride deficient diet, bulimia, cyclic vomiting, congenital chloride diarrhea and abuse of laxatives. Low chloride content in urine except in diuretic use exclude BS in these cases.

Management:
Antenatal Diagnosis: Antenatal diagnosis should be done in a suspected case of unexplained polyhydramnios with history of consanguinity and previous affected sibling with Bartter's like illness. Identification of genetic mutation in sample obtained by amniocentesis at 18 weeks of gestation gives unequivocal diagnosis (6). Amniotic fluid biochemistry showing elevated chloride levels also helps in diagnosis.

Based on assumption of hyperprostaglandinism, antenatal and postnatal treatment of these patients with prostaglandin synthetase inhibitor, Indomethacin has shown promising results. Indomethacin should be started antenatally in a genetically diagnosed patient. Other causes of polyhydramnios like fetal intestinal losses, esophageal atresia should be excluded before initiation of therapy as in these cases indomethacin may aggravate the situation. Indomethacin therapy should be monitored carefully by fetal echocardiography and maternal serum indomethacin level because of complication like premature closure of ductus arteriosus, oliguric renal dysfunction, necrotizing enterocolitis, and ileal perforation (6). A low dose of indomethacin (0.5mg/kg/dose every 12 hourly) from 26-31 weeks of gestation is sufficient to arrest the progression of polyhydramnios. Other prostaglandin synthetase inhibitors like ibuprofen, acetylsalicylic acid have also been proved effective.

BS baby inspite of intrauterine polyuria and electrolyte loss, is well hydrated at birth because of compensation by placenta. But postnatally there is rapid loss of electrolytes and fluids from the body. So immediate replacement is must. Indomethacin should be started in a low dose (0.2 mg/kg/day) as there is risk of acute renal failure and necrotizing enterocolitis.

Close monitoring of serum creatinine, urinary prostaglandin and serum indomethacin level is mandatory

Table 1: Various types of Bartter's Syndromes and their characteristics

	Antenatal BS I	Antenatal BS II	Classic BS III	BS IV (BSND)	Gitelman's Variant
Channel	NKCC2	ROMK	CIC-Kb	CIC-Kb/CIC-Ka	NCCT
Location	TAL	TAL, CD	TAL, DCT	TAL, Inner ear	DCT
Gene	SLC12A1	KCNJ1	CLCNKB	BSND	SLC12A3
Chromosome	15q15-21	11q24	1p36	1p31	16q13
Polyhydramnios	Present	Present	Usually absent	Present	Absent
Gestational Age	Preterm	Preterm	Term	Preterm	Term
Age of onset	Antenatal	Antenatal	<1year	Antenatal	6-13 years
Symptoms	Polyuria	Polyuria	Hypokalemia Failure to thrive	Polyuria, Deafness	Hypokalemia, Tetany
Urine Ca excretion	High	High	Moderate	High	Hypocalciuria
Nephrocalcinosis	Present	Present	Usually absent	Present	Absent
Magnesium	Normal	Normal	Low or Normal	Normal	Always Low
Prostaglandin level	Increased	Increased	Increased	Increased	Near Normal
Prostaglandin Excretion	Increased	Increased	Increased	Increased	Normal

can then be titrated to achieve adequate response. This therapy has shown to decrease polyuria, renal salt wasting, hyperprostaglandinuria, hypercalciuria and nephrocalcinosis.

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