Bartter Syndrom

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- Introduction
- Pathogenesis
- Diagnosis
- Clinical Presentation
- Diffrential diagnosis
- Treatment
- Follow up
- Pregnancy considerations

- Introduction:
- - In 1962, Bartter and coworkers described disease.
- -With hypokalemic metabolic alkalosis, hyperreninemic hyperaldosteronism.
- - Normal blood Pressure, as well as hyperplasia and hypertrophy of the juxtaglomerular apparatus.
- - Bartter syndrom is a genetically heterogeneous disorder affecting the Loop of henle.
- - That typically manifests during the neonatal Period and is associated with hypercalciuria and nephrocalcinosis

- Brenner 2020

- Pathogenesis:
- - Five different forms (B5 1-5), based on molecular genetics, have been identified to date.
- - BS is a potentially Life- threatening condition necessitating rapid diagnosis and therapy.
- - The Primary molecular defect in all types of BS Leads to impaired salt reabsorption in the thick asending Limb of the Loop of henle.
- - mutations result in renal tubular salt wasting with activation of the renin angiotensin system and consequent hypokalemic and hypochloremic metabolic alkalosis.

- In addition, the tubuloglomerular Feedback is altered at the Level of the macula densa, which, Under Physiologic Conditions, senses Low tubular chloride concentratiobs in conditions of Volume contractions.

Ki 2021

- Contineuse
- -This activates cyclooxygenases (Primarily cox-2) to produce high amounts of Prostaglandins (Primarily Prostaglandin E 2).
- - which in turn stimulate renin secretion and aldosterone Production, in attempt to reestablish normal intravascular volume and glomerular perfusion.

- - Impaired salt reabsorbption in the TAL has 2 consequences: (i) a reduction of
- calcium reabsorption with hypercalciuria and progressive medullary nephrocalcinosis and (ii) a reduction or complete blunting of the osmotic gradient in the renal medulla, causing isosthenuria, i.e, an impaired ability to dilute or Concentrate the urine

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Table 1 | Molecular genetics of Bartter syndrome

Characteristic	Type 1	Type 2	Type 3	Type 4a	Type 4b	Type 5
OMIM	601678	241200	607364	602522	613090	300971
Gene	*SLC12A1*	*KCNJ1*	*CLCNKB*	*BSND*	*CLCNKA* + *CLCNKB*	*MAGED2*
Protein	NKCC2	KCNJ1 (ROMK or Kir1.1)	ClC-Kb	Barttin	ClC-Ka + ClC-Kb	MAGE-D2
Inheritance	AR	AR	AR	AR	AR	XLR

AR, autosomal recessive; OMIM, Online Mendelian Inheritance in Man; XLR, X-linked recessive.

کدام کلاس سندرم بارتر اختلال در پروتئین Barttin می باشد؟

الف) تیپ II

ب) تیپ IVa

ج) تیپ IVb

د) تیپ V

کدام کلاس سندرم بارتر به صورت X-Link انتقال می یابد؟

الف) تیپ III

ب) تیپ IV

ج) تیپ V

د) تیپ I

: Diagnosis - •

- -The diagnosis of BS is primarily base on clinical, biochemical and Sonographic findings .
- -Even if the diffrent subtypes of BS can usually be characterized clinically We recommend genetic analysis for confirmation
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- Antenatal diagnostic work-up :
- - Early Polyhydramnios of tetal origin should raise the clinical suspicion of BS.
- - In Principle, there are 2 possible options to confirm the diagnosis : (i) Prenatal genetic testing and (ii) biochemical analysis of amniotic fluid.
- - Both measures are invasive and carry the risk of procedure-related complication.
- - Howere, whenever Prenatal diagnosis is indicated, we consider genetic testing to be the most reliable method.
- - In situations, where prenatal genetic testing is not available or diagnostic, the assessment of the Bartter index. (total Protein ×alfa-fetoprotein) may be considered.

- Postnatal diagnostic work-up:
- - postnatally, a diagnosis of BS should be considered in the presence of renal Salt wasting, Polyuria rapid weight loss, and signs of dehydration.
- - Failure to thrive, recurrent Vomiting, repeated fever, hypochloremic and hypokalemic metabolis alkalosis, and nephrocalcinosis

- - Evaluation of medical history including polyhydramnios, Premature birth, growth Failure, and family history.
- - Biochemical parameters: serum electrolytes (sodium, chloride, Potassium, Calcium, magnesium), acid-base status, renin, aldosterone, creatinine, fractional excretion of chloride, and urinary Calcium – Creatinine ratio.

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- Continue…
- - Renal ultrasound to detect medullary nephrocalcinosis and / or kidney stones.
- - we recommend confirming the clinical diagnosis of BS by means of genetic analysis whenever possible.
- -We suggest offering genetic counseling for families with Probands with confirmed Clinical and / or genetic diagnosis of BS.
- - We do not recommend tubular function tests with furosemide or thiazides for Patients with suspected BS if genetic testing is accessible
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- Clinical characteristics of diffrent types of BS :
- Age at presentation:
- -BS causes polyhydramnios, Leading to premature birth in the majority of patients.
- - Polyhydramnios typically develops between the 20th and 30th weeks of gestation.
- -In BS4 and BS5, Polyhydramnios is typically observed earlier than in BS1 and BS2
- -BS3 usually manifests Later in Life. Nevertheless, a prenatal Presentatio does not exclude BS3.

- The vast majority of patients with BS3 are diagnosed after the age of 1 year

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- salt wasting:
- - After birth, the first symptom is often hypovolemia from renal salt loss.
- - Hypochloremic and hypokalemie metabolic alkalosis may not be present during the first days of life.
- - In fants with BS2 often have transient neonatal acidosis and hyperkalemic
- and, on average, hypokalemia and alkalosis are Less Pronounced during Follow-up.
- - In some Patients with BS3, hypomagnesemia may be present.

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- Calciuria and nephrocalcinosis:
- - Hypercalciuria with subsequent nephrocalcinosis occuring after 1-2 months
- of Life is a typical feature of BS1 and B52.
- - In contrast, patients with BS3 and BS4 usually have normocalciuria ,although hypercalciuria may occur.
- - Interestingly, hypocalciuria has also been reported in patients with BS3, and these patients minic the phenotype of GS.
- - In transient BS5, hypercalciuria may be observed, but nephrocalcinosis a rare finding.

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Table 2| Main clinical and biochemical characteristics of different types of Bartter syndrome

Characteristic	Type 1	Type 2	Type 3	Type 4a	Type 4b	Type 5
Age at onset	Prenatally	Prenatally	0–5 years	Prenatally		Prenatally
Polyhydramnios	Severe	Severe	Absent or mild	Severe		Very severe
Gestational age at birth, wks, median (IQR)	32 (29–34)	33 (31–35)	37 (36–41)	31 (28–35)		29 (21–37)
Leading symptoms	Polyuria, hypochloremia, alkalosis, hypokalemia	Polyuria, hypochloremia, alkalosis, transient neonatal hyperkalemia	Hypokalemia, hypochloremia, alkalosis, failure to thrive	Polyuria, hypochloremia, alkalosis, hypokalemia		Polyuria, hypochloremia, alkalosis, hypokalemia
Calcium excretion	High	High	Variable	Variable		High
Nephrocalcinosis	Very frequent	Very frequent	Rare, mild	Rare, mild		Rare, mild
Plasma Cl/Na ratio	Normal	Normal	Decreased	Decreased		Increased
Other findings			Mild hypomagnesemia	Deafness, risk for CKD, ESRD		Large for gestational age, transient disease

CKD, chronic kidney disease; ESRD end-stage renal disease; IQR, interquartile range.
Data from Komhoff and Laghmani[20] and Legrand *et al.*[21]

- کدام کلاس سندرم بارتر با transient neonatal hyperkalemia همراه است؟
- الف) تیپ Ⅲ
- ب) تیپ Ⅳ
- ج) تیپ Ⅱ
- د) تیپ Ⅴ
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- کدام کلاس سندرم بارتر با Deafness همراهی دارد؟
- الف) تیپ II
- ب) تیپ IV
- ج) تیپ V
- د) تیپ I

- Diffrential diagnosis:
- - congenital chloride diarrhea can be confused with BS.
- - Pseudo - Bartter syndrome is occasionally observed in cystic fibrosis because of salt loss in sweat.
- - Presentation beyond infancy, especially in adolescence or even adulthood
- (most often BS3), makes GS a primary consideration in those patients with
- hypocalciuria and / or hypomagnesemia.
- - patients with hepatocyte nuclear factor 1B nephropathy may also present with hypokalemiac alkalosis and hypomagnesemia

- Contineu...
- -some Patients with BS primarily present with nephrocalcinosis and/or urolithiasis. a young age at onset of kidney stone disease should raise the Clinical suspicion of a specific underlying cause, including (in complete) distal renal tubular acidosis.
- - If the presenting sign is hypokalemia, the initial diffrential diagnosis is wide.
- - It is important to distinguish renal from gastrointestinal potassium Loss and potassium shifts.
- - If Primary hyperaldosteronism and diuretic and or laxative use or abuse are excluded.

Gene	Associated disorder (MIM)
SLC12A1[a]	BS1 (601678)
KCNJ1[a]	BS2 (241200)
CLCNKB[a]	BS3 (607364)
	BS4b (613090)
CLCNKA[a]	BS4b (613090)
BSND[a]	BS4a (602522)
MAGED2[a]	BS5 (300971)
SLC12A3[a]	Gitelman (263800)
CASR	ADH (601198)
KCNJ10	EAST/Sesame (612780)
SLC26A3	CCD (214700)
CLDN10	HELIX (617671)
SCNN1A	PHA1B (264350)
SCNN1B	Liddle syndrome (177200)
SCNN1G	
NR3C2	PHA1A (177735)
HSD11B2	AME (218030)
CYP11B1	HALD1 (103900)
CLCN2	HALD2 (605635)
KCNJ5	HALD3 (600734)
CACNA1H	HALD4 (607904)

ADH, autosomal dominant hypocalcemia; AME, apparent mineralocorticoid excess; BS, Bartter syndrome; CCD, congenital chloride diarrhea; EAST, epilepsy, ataxia, sensorineural deafness, tubulopathy; HALD, familial hyperaldosteronism; HELIX, hypohidrosis, electrolyte imbalance, lacrimal gland dysfunction, ichthyosis, xerostomia; MIM, Mendelian Inheritance in Man; PHA, pseudohypoaldosteronism.

[a]Genes in rows 2–8 should be included in a minimal diagnostic panel, i.e., the genes underlying BS, as well as Gitelman syndrome, which can be difficult to distinguish clinically from BS3. The remaining list also includes genes, which can have phenotypic overlap with BS. BS2 can mimic pseudohypoaldosteronism type 1 (PHA1) in the

Polyhydramnios of fetal origin	Aneuploidia	Abnormal karyotype
	Gastrointestinal tract malformation	Variable, empty stomach
	Congenital chloride diarrhea	Dilated intestinal loops
Salt loss	Pseudohypoaldosteronism type I	Metabolic acidosis, hyperkalemia
Salt loss with hypokalemic alkalosis	Congenital chloride diarrhea	Low urinary chloride
	Pseudo-Bartter syndrome, e.g., in CF	Low urinary chloride
	Gitelman syndrome	Hypocalciuria, hypomagnesemia
	HNF1B nephropathy	Renal malformation, cysts, MODY5, hypomagnesemia
	HELIX syndrome	Hypercalcemia, hypohidrosis, ichthyosis
	Autosomal dominant hypocalcemia	Hypocalcemia, seizures
	EAST/SeSAME syndrome	Ataxia, seizures, deafness, developmental delay
	Surreptitious vomiting	Low urinary chloride
	Surreptitious laxative use	Low urinary chloride
	Surreptitious diuretic use	Highly variable urinary chloride
Hypokalemic alkalosis without salt loss	Primary hyperaldosteronism;	Hypertension, low renin
	Apparent mineralocorticoid excess	Hypertension, low renin/ aldosterone
	Liddle syndrome	Hypertension, low renin/ aldosterone
Nephrocalcinosis	Distal renal tubular acidosis	Metabolic acidosis
	Proximal tubular defects	No metabolic alkalosis
	Familial hypomagnesemia/ hypercalciuria	No hypokalemic metabolic alkalosis, CKD
	Apparent mineralocorticoid excess	Hypertension, low renin/ aldosterone

- Therapy:
- Prenatal therapy:
- - Pragnancies complicated by Polyhydramnios are at risk of adverse outcomes ,especially preterm delivery and complication of Premature birth.
- - serial amniocenteses are commonly used in the intention of Prolonging pregnancies, but the benefits of this strategy have not been evaluted in Prospective studies.
- - maternal treatment with NSAIDS can be considered.
- - however, the treatment carries significant risks for the fetus, especially of fetal ductus arteriosus constriction.
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- Contineu…
- - Therefore, close monitoring with the use of fetal echocardiography is mandatory
- in all cases of maternal NSAID therapy.
- - other reported complications include neonatal intestinal perforation and necrotizing enterocolitis.
- - To date, only a few cases of BS with positive outcome after serial amniocentesi
- and for Prenatal indomethacin therapy have been reported.
- - If Prenatal intervention is considered, a multidisciplinary perinatal team is mandatory, including "a maternal-fetal medicine specialist, a neonatologist a pediatric cardiologist, and a pediatric nephrologist.
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- Post natal therapy:
- Salt Supplementation:
- -Supplementation with sodium chloride constitutes a physiologic treatment that can support extracellulary volume and improve electrolyte abnormalities.
- - At least 5–10 mmol /kg/ day been recommended.
- - Beyond infancy, some of this supplementation may be provided by Salt Craving and high spontaneous salt intake that is typical for BS.
- - we recommend against salt supplementation in Patients with hypernatremic dehydration and a concomitant urine osmolality Lower than plasma or a history thereof.

- potassium supplementation:
- - If Potassium is supplemented, Potassium chloride should be used.
- - Potassium salts (e.g, citrate) should be avoided because they potentially
- worsen the metabolic disturbance by aggravating the alkaLosis.
- - Potassium -rich food should be advised, with the caution that some of them contain high amounts of carbohydrates and calories.
- - The target Level for Plasma potassium is not exactly known but a reasonable target Level may be 3 $\frac{\mathrm{mmoL}}{L}$.

- magnesium supplementation:
- - If magnesium needs to be supplemented (mainly in patients with BS3), oral administration of magnesium salts should be preferred.
- - It is important to note that organic salts (e.g, aspartate, citrate, Lactate) higher bioavailability than magnesium oxide or hydroxide.
- - Exact target levels for Plasma magnesium in BS are unknown but a Level > 0.6 $\frac{\mathrm{mmoL}}{L}$ appears to be reasonable.
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- NSAIDS:
- - Pharmacologic suppression of prostaglandin formation addresses the underlying
- Pathophysiology, and multiple clinical observational studies have shown benefit in the form of improved growth and electrolyte profile.
- - Commonly used NSAIDs in BS are indomethacin (1-4 mg/kg/day 3-4 doses), ibuprofen (15-30 mg/kg daily in 3 doses), and celecoxibe (2-10 mg/kg/day in 2 doses).
- - Currently, there is insufficient evidence of recommend a Specific NSAID in BS, and the risks of gastrointestinal and Cardiovascular side-effects need to be considered individually.
- - chronic use of NSAIDs should be considered carefully in each individual Patient, and tapering or cessation may be indicated in stable Patients.
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- Gastric acid inhibitors :
- - If non selective cox inhibitors are prescribed, they should be accompanied by gastric acid suppression.
- - If proton pump inhibitors are used, there is a small risk of proton pump inhibitor-associated hypomagnesemia ·
- - Conversion to H_2 blockers or other antacids (or to a cox-2 inhibitor) is recommended in those instances.
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- Supportive treatment:
- - Growth failure is a failure is a common complication of BS and often part of the initia Presentation.
- - Dietetic support is important to maximize caloric intake and facilitate optimal growth.
- - Especially in infants and young children, tube feeding may need to be Considered.
- - A feeding tube will help not only to achieve adequate caloric intake, but also the administration of salt supplements.
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- K-sparing diuretics, ACEIS, ARBS and thiazides:
- - we do not recommend routine use of these drugs.
- - Instead, they should be considered carefully in individual cases and be indicated in those who have severe symptoms from the electrolyte abnormalities despite maximization of routine treatment with NSAIDS and salt supplements.
- - Thiazides are occasionally used in an attemp to reduce calcium excretion.
- - Thiazides in BS may lead to Life threating hypovolemia and should not be routinely administered

- Growth hormone:
- - Growth failure with growth hormon (GH) deficiency in BS has been reported.
- - Elevated systemic Prostaglandins may contributed to growth failure.
- - In one report, GH deficiency failed to respond to recombinant human GH supplementation until treatment with a Cox inhibitor was commenced.
- - Thus before commencement of recombinant human GH, optimization metabolic control should be attempted.
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- Follow – up:
- Frequency and setting of visits:
- - Patient with BS should be followed in specialized centers with experience in
- renal tubular disorders to facilitate best medical care.
- - Infants and young children with BS should be seen at least every 3-6 months, depending on severity of clinical Problems, to ensure adequate metabolic control, growth, and Psychomotor development.
- - Older children with an established therapy and stable condition should be seen at least every 6-12 months.
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- Contineu…
- - Adult Patients a should be seen every 6-12 months.
- - Evaluating QOL using age-appropriate scales from age 5 years on ward at 2-year intervals.
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- Follow-up of children:
- - At each follow-up visit, focusing the history and examination on dehydration, degree of Polyuria, signs of muscular weakness, growth, and Psychomotor development.
- - Biochemical work-up should include acid-base status (either by blood gas of by measurement of venous total (02), serum electrolytes (include bicarbonate, chloride and magnesium), renal function, PTH and urinary calcium excretion.
- - Assessing urine osmolality to test for secondary NDI.
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- Contineu…
- - Performing renal ultrasound at least every 12-24 months to monitor nephrocal cinosis, the occurrence of Kidney stones, and signs of secondary obstractive
- uropathy.
- - For Children with growth retardation despite intensified efforts for metabolic Central Considering growth hormon deficiency.
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- Follow-up of adults:
- - At each follow-up visit, focusing the history and examination on dehydration,
- degree of polyuria, Signs of muscular weakness, fatigue, and Palpitations.
- - Biochemical work-up should include acid-base status (either by blood gas or by
- assurement venous total co2), serum electrolytes (including bicarbonate, chloride, and magnesium), renal function, PTH, Urinary calcium excretion, and microalbuminuria.
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- Contineu…
- - Performing renal ultrasound at Least every 12-24 months to monitor nephrocalcinosis, the occurrence of kidney stones, and signs of secondary obstructive Uropathy.
- - performing further cardiology work-up in Patients complaining of Palpitations or syncope.
- - for pregnant women or those Planning to become pregnant, the timely institution of a joint managment plan involving nephrology and obstetrics.
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- Pregnancy Considerations:
- - During normal pregnancy, serum potassium Levels decrease by 0.2 – 0.5 $\frac{mmoL}{L}$ around midgestation.
- - In pregnant women with BS, timely institution of a Joint management Plan involving and obstetrics as well as appropriate adaptations in therapy is mandatory.
- - During pregnancy, the target Level for Plasma Potassium is unknown, but a level of 3 $\frac{\mathrm{mmoL}}{L}$ has been suggested with the explicit acknowledgement that this may not be achievable in some patients.
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- Contineu…
- - In patients with BS, the occurrence of hyperemesis gravidarum may be particulare dangerous owing to the subsequent electrolyte disturbances that may necessitate early Parenteral fluid and electrolyte supplements.
- - Pregnant women with BS should be informed about increased requirements of
- electrolyte supplements, that renin-angiotensin system blockers are contraindicated and that NSAIDS are discouraged during pregnancy.
- - monitoring of Plasma electrolyte Levels is advised during labor.
- therefore, delivery in hospital might be considered to reduce risks of maternal complications.

- Contineu…
- - The overall outcome for women with BS and their infants described to date is favorable.
- - After delivery, the treatment of the mother may return to baseline supplementation

Thank you