

AN OVERVIEW ON BARTTER SYNDROMES: LITERATURE REVIEW

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ABSTRACT

Background: Bartter's syndrome (BS) is a group of kidney genetic tubulopathies, which presents with hypokalemia, hyperaldosteronism, metabolic alkalosis, with juxtaglomerular apparatus hyperplasia. These genetic defects usually involve proteins crucial in tubular fluid reabsorption in the thick ascending limb part of Henle's loop. This inherited renal tubular disease affects around 1 person in a million of the general population. Unfortunately, this disease is associated with higher mortality in the antenatal and neonatal periods. **Objectives:** We aimed to review the literature regarding the pathophysiology of Bartter's syndrome, clinical features, risk factors, diagnosis, and the management of this disease. **Methodology:** PubMed database was used for articles selection, papers were obtained and reviewed. **Conclusion:** Bartter syndrome is not curable yet, however, management of the clinical signs and symptoms is achievable. Physician's clinical suspicion, good history taking, and physical examination skills are paramount to diagnose this syndrome along with some key tests. The importance of early diagnosis and management is immeasurable since deadly complications (such as sudden cardiac death), and long-term complications (like short stature) can be avoided. Nevertheless, a new basis for treatment based on treating the defected genes are being developed and the development of personalized therapeutic options for this syndrome may provide a permanent cure for these.

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Introduction

Bartter's syndrome (BS) is a group of kidney genetic tubulopathies discovered in 1962 by a physician with the same name. This syndrome presents with hypokalemia, hyperaldosteronism, metabolic alkalosis, with juxtaglomerular apparatus hyperplasia. Overall, there are five types of BS and different causative genetic defects are the reason behind the classification. These genetic defects involve proteins crucial in tubular fluid reabsorption in the thick ascending limb part of Henle's loop. [1, 2] This rare inherited renal tubular disorder affects around 1 person in a million of the general population. However, it can be noted in a higher frequency in some populations such as in Costa Rica and Kuwait with 1.2 and 1.7 cases in every 100,000 people, respectively. Unfortunately, this disease is associated with higher mortality in the antenatal and neonatal periods, mainly because failure to thrive is common in these patients. [3, 4] This paper will discuss this syndrome with its types, pathophysiology, clinical features, diagnosis, and management.

Methodology

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PubMed database was used for articles selection, and the following keys were used in the mesh ("Bartter Syndromes"[Mesh] AND ("Diagnosis"[Mesh] OR "Management"[Mesh])). In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics; Bartter Syndromes' evaluation, management, and diagnosis. Exclusion criteria were all articles that did not have one of the inclusion criteria's topics as the primary endpoint.

Review

Bartter's syndrome has multiple pathologies that can be noted with elevated prostaglandin E2 (PGE2) production, renin and aldosterone levels, low chloride, and salt and fluid loss. These changes can present with metabolic alkalosis but with usually a normal blood pressure (low in some) and growth delay. [1, 5] Multiple classifications are available, the clinical-based one is common, with three main clinical types; a neonatal (or antenatal) variant, a classic variant, and Gitelman syndrome. However, a more recent and widely-used classification based on the underlying genetic defect has been adapted. This classification divides this disease into 5 types from type 1 (I) to type 5 (V). [6]

Causes and Types:

Generally, all types of this disease happen due to an autosomal resistive defect in the coding of genes with one exception mentioned later. In type 1 (I) of the Bartter syndrome, mutations in SLC12A1, which is the sodium-chloride-potassium co-transporter gene happens. This type presents clinically as the antenatal variant. [7] In type 2 (II), the mutations involve the ROMK gene and will present clinically as antenatal or neonatal Bartter syndrome. Type 3 (III) results from mutations leading to loss of function in the CLCNKB gene, encoding the kidney-specific- basolateral chloride channel (CIC-Kb). This channel is involved in the sodium chloride reabsorption that takes place in the renal tubule. This type will present clinically as the classic type of Bartter syndrome and can be diagnosed in infancy or early childhood. Nevertheless, type 4 (IV) has 2 main causes, and thus some resources further classify it into type 4 A, and type 4 B. In type 4 A, the main genetic defect is a loss of function affecting the BSND gene which encodes an important beta subunit (barttin) for chloride channels (CIC-Kbs). Type 4 B has different mutations affecting both CLCNKB and CLCNKA genes, which will affect two basolateral chloride channels (CIC-Ka and CIC-Kb). Both types will target mainly the channels in Henle's loop, distal convoluted tubule, and cortical collecting ducts of the kidney. [8] Moreover, the inner ear has these channels as well (along with CIC-K isoforms), contributing to potassium secretion into the endolymph which is done by the marginal cells of the stria vascularis, and type 4 mutations affect them as well. [9] The nature of CLCNKB mutations is very different, and up to 50 types have been recognized affecting barttin binding sites, dimer interface, C-terminal region, and many more. Nevertheless, the most common defect is the deletion of the whole CLCNKB gene. Most CIC-Kb mutations resulted in a more than 60% reduction in chloride current mainly because of the change in expression of the plasma membrane of the channel. Nevertheless, barttin mutations drastically reduce the function of CIC-K channels and reduce transepithelial chloride transport. Even though mutations altering channel gating are not frequent, the prognosis of these patients is affected by the mutation type. Severe mutations are associated with earlier diagnosis of less serum chloride concentration, higher urine calcium excretion rate, and worse prognosis. [10, 11]. Type V is usually less severe clinically and is due to mutations in the extracellular calcium-sensing receptor (CaSR). [12] However, recently, mutations in melanoma-associated antigen-D2 (MAGE-D2) have proven to be associated with a transient variety of antenatal BS. Some reports also referred to this variant as type V BS.24 MAGE-D2 is an X-chromosome related gene, so patients having this mutation are predominantly males. [13, 14]

Pathophysiology:

Bartter syndrome affects kidneys and causes tubular salt-wasting where reabsorption of sodium and chloride does not happen. This process usually occurs in the ascending limb of the loop of Henle. The absence of this process will result in a higher salt and water from the body, resulting in overall volume depletion. As a result, the renin-angiotensin-aldosterone system (RAAS) will activate, which will cause secondary hyperaldosteronism. Moreover, with long-term activation, hyperplasia involving juxtaglomerular apparatus occurs, thus renin levels increase. The high sodium levels (in the distal portion) will enhance distal convoluted tubule sodium reabsorption, thus a higher exchange rate with potassium or hydrogen ion (negatively charged). This will lead to a higher loss of potassium and hydrogen. Moreover, less chloride reabsorption results in less exchange with bicarbonate for chloride, thus, more bicarbonate retention happens. These changes may leave the patient with low levels of potassium and metabolic alkalosis. [15]

The kidney's ability to concentrate and dilute urine is affected as well in BS. Exposed concentration mechanisms happen due to defective sodium absorption in the loop of Henle as mentioned earlier. Other factors including; hypokalemia, polyuria, and elevated prostaglandin E2 levels have some implications as well. Moreover, abnormal sodium chloride transport affects the electrochemical gradient. Under normal situations, calcium and magnesium are being absorbed (paracellularly) due to a positive charge in the lumen, which happens due to the reabsorption of chloride ions (negatively charged). This will affect other ions, such as magnesium reabsorption, leading to increased urinary loss of both, calcium and magnesium. Due to high levels of calcium in the urine, one of the common pathologies noted in BS patients is nephrocalcinosis. [16]

Clinical Features:

Clinicians need to take a thorough history either from parents or the patient him/herself. Family history is crucial in these cases and will give the physician a big hint towards diagnosis. One of the commonly noted family histories in these patients

is nephrocalcinosis. Bartter syndrome usually presents in children, however, some adolescents may still present with this syndrome without being previously diagnosed. History taking may reveal many symptoms including growth delays (failure to thrive), polyuria, polydipsia, vomiting, dehydration, constipation, cramps, deafness, and kidney stones. In physical examination, the physician may notice some features, such as a prominent forehead, large eyes, protruding ears, drooping mouth corners, and strabismus. If the patient has deafness, the clinician may be able to recognize it as a sensorineural type. Usually, patients will have either normal or low blood pressure, but long-standing cases may have elevated blood pressure. Antenatal Bartter syndrome (e.g. type 3) cases can present with polyhydramnios, which is secondary to intrauterine polyuria and will usually be delivered prematurely. After birth, some common findings are sensorineural deafness, fever, polyuria, vomiting, and diarrhea, which will lead to dehydration. Less severe form (Gitelman syndrome) will usually present with hypocalciuria, hypomagnesemia, without polyuria. However, type IV (both variants) is a more severe variant with all the features and usually is the type presenting with congenital sensorineural hearing loss. MAGE-D2 related BS type is characterized usually by an early onset of severe polyhydramnios and symptoms are resolved on their own after birth. Differential diagnoses for such syndrome are multiple and must be eliminated by the clinician. Diuretic abuse and surreptitious vomiting history must be taken. Aminoglycosides may cause BS like syndrome, thus, the clinician needs to acquire about any recent antibiotics usage. Other differential diagnoses include hyperprostaglandin E syndrome, familial hypomagnesemia (with hypercalciuria/nephrocalcinosis), and mineralocorticoid excess. Some other diseases that may present with some similar features like pyloric stenosis, cystic fibrosis, Gullner syndrome, hypomagnesemia, congenital chloride diarrhea, hypochloremic alkalosis, and hypokalemia must be excluded as well. [17, 18]

Diagnosis:

A good history and physical exam can lead to a good clinician towards this syndrome once the identification of characteristic symptoms is done. However, some tests can make the physician build a more concrete picture of the diagnosis. Serum electrolyte profile and acid-base studies will be abnormal and findings of hypokalemia and metabolic alkalosis are the most common. Other findings include high renin and/or aldosterone levels with decreased magnesium, and phosphate levels. Urine electrolytes test is done as well and may reveal elevated potassium, sodium, and PGE2 excretion. Some tests, like spot urine chloride concentration, can differentiate BS from surreptitious vomiting. In Bartter syndrome, it is elevated (more than 35 meq/L), and in vomiting cases, it is lower than 25 meq/L. Generally, in early cases, the functional tests of the kidney are all normal and preserved as opposed to late cases, which are associated with chronic renal disease. Gitelman syndrome is not associated with high calcium excretion in urine and thus 24-hour urine study helps to rule it out. In antenatal and neonatal Bartter syndrome, polyhydramnios and intrauterine growth retardation can be detected with ultrasound and amniotic fluid chloride levels can be elevated. Further tests can be carried out including, abdominal radiographs, intravenous pyelograms (IVPs), renal ultrasonograms, and/or spiral CT scans in order to document nephrocalcinosis. Moreover, and in special cases, genetic testing is done when the physician needs to rule out specific mutations. [1, 8, 13, 17]

Management:

The most important goal to achieve by a clinician is the replacement of all the lost fluid and electrolytes, in order to reduce the mortality and morbidity in these patients. However, this syndrome is difficult to treat and still has no complete cure. In the neonatal period, the physician may need to start a saline infusion. Generally, oral potassium supplements (e.g. kcal 25 to 100 mmol/day) are enough to normalize potassium levels in serum. Similarly, oral ACE inhibitors, and/or angiotensin receptor blockers (ARB) can decrease angiotensin II and aldosterone levels. This will result in less proteinuria, and -in some cases- increase serum potassium. For increased PGE2 levels, multiple options such as spironolactone, amiloride (with a dose of 5 to 40 mg per day), and NSAID (e.g. indomethacin) can help. If hypomagnesemia is found, the clinician shall consider magnesium supplementation, as it may worsen the potassium wasting. In aminoglycoside BS like syndrome, only close monitoring and resupply of electrolytes is indicated, with full recovery achieved within 2 to 6 weeks. [18-20]

With new molecular and genetic breakthroughs, the possibility to target this syndrome mutation directly is appealing. This approach can ensure a definitive, specific, and safer therapy option in these patients. However, these are still not available and need a full understanding of all biophysical characterization of mutations to reveal all the specific BS channel functional defects [21].

Untreated Bartter syndrome is associated with significant morbidity and mortality. Some complications such as cardiac arrhythmia, sudden death (from electrolyte imbalances), and chronic renal disease must be considered in these patients. However, tubular abnormalities that are characterized in these patients are usually resolved after kidney transplantation with almost no recurrence. Generally, the more severe the mutations are the worse the prognosis is, however, with tight compliance to treatment plan most patients lead to a normal life. Thus, early recognition and treatment are crucial to prevent long term complications such as growth retardation. [1, 8]

Conclusion

Bartter syndrome includes multiple rare genetic disorders that primarily affect the kidney (and inner ear). This disease is incurable yet, however, management of the clinical signs and symptoms is achievable. Thus, the physician's clinical suspicion, good history taking, and physical examination skills are paramount to diagnose this syndrome along with some

key tests. Early diagnosis and management are paramount since deadly complications such as sudden cardiac death, and long term complications like short stature can be avoided. Nevertheless, a new basis for treatment based on treating the defected genes is being developed and the development of personalized therapeutic options for this syndrome may provide a permanent cure for these patients.

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