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Case Report

Complexities of Bartter Syndrome Type III: A Case Study in Jordan

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Abstract

Bartter Syndrome (BS) is a genetic disorder affecting the renal tubules, leading to elevated levels of renin, angiotensin, and aldosterone, along with metabolic alkalosis, while maintaining normal blood pressure. It is also associated with laboratory abnormalities such as hypocalcemia, hypokalemia, hypomagnesemia, and hyponatremia, which may result in neurological complications including seizures and loss of consciousness. These findings necessitate consideration of important differential diagnoses such as Gitelman syndrome and cystic fibrosis, underscoring the importance of confirming the diagnosis of this serious condition, giving it appropriate attention, and initiating early treatment to prevent advanced complications. We report the case of a 36-year-old Jordanian male with a medical history of Bartter Syndrome and chronic kidney disease, who presented to the emergency department in a coma with generalized seizures due to severe electrolyte imbalances. His condition was further complicated by a genetic predisposition and a family history of Bartter Syndrome, with genetic testing confirming mutations in the CLCNKB gene. This rare case of Bartter Syndrome type III, in which the patient progressed to the stage of hemodialysis, illustrates the complexities of diagnosis and management, and emphasizes the importance of continuous care and regular follow-up.

Keywords: Bartter Syndrome; Chronic Kidney Disease; Loop of Henle; CLCNKB; Antenatal Bartter Syndrome; Classical Bartter Syndrome

Key Clinical Messages:

1. Despite the rarity of Bartter Syndrome (with an incidence of approximately 1 in 1,000,000 people), every possible diagnosis must be carefully considered by thoroughly investigating all accompanying symptoms in order to avoid potential complications.

2. Bartter Syndrome has a hereditary pattern of transmission, which was confirmed in our study by the presence of a family history between the patient and his brother. This highlights the importance of genetic testing, particularly through analysis of the CLCNKB gene, to confirm the diagnosis of Bartter Syndrome type III.

3. Due to the persistent loss of electrolytes such as potassium, calcium, and magnesium, patients are prone to neurological complications including seizures, in addition to other potential consequences. Therefore, urgent emergency intervention to correct electrolyte imbalances is essential and can be life-saving.

4. Finally, this case underscores the importance of multidisciplinary collaboration between specialties such as internal medicine, nephrology, nutrition, and nursing, in order to achieve the best possible outcome for both the patient and the disease management.

Background

Bartter Syndrome (BS) was first discovered in 1962 by Bartter. It is an autosomal recessive disorder of the renal tubules characterized by a set of laboratory abnormalities, most notably elevated renin, angiotensin, and aldosterone levels, along with metabolic alkalosis and normal blood pressure [1]. The estimated prevalence of this syndrome is approximately 1 per million individuals [2]. Clinically, Bartter Syndrome is classified into classical Bartter Syndrome (cBS) and antenatal Bartter Syndrome (aBS) [3]. Accordingly, the symptoms and their severity vary depending on the affected age group; adults primarily suffer from polyuria and fatigue, while polyhydramnios and hypovolemia are the main symptoms in aBS [4]. To our knowledge, this study presents the first documented case in Jordan of Bartter Syndrome type III in an adult patient. The case involves a 36-year-old male who presented with generalized seizures and coma as a result of severe electrolyte imbalances. The complexity of managing such chronic

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conditions, especially in the presence of concurrent kidney disease, is highlighted in this review.

Case Presentation

The patient is a 36-year-old Jordanian male who was diagnosed with Bartter Syndrome at the age of 26. He presented to the emergency department with generalized seizures and a state of coma, raising immediate concerns regarding significant electrolyte disturbances. His medical history is notable for chronic kidney disease (CKD) (see Figure 1), requiring regular dialysis for the past three years, with treatments conducted three times a week. The patient denied any smoking history and reported no prior instances of diabetes or hypertension. However, he had experienced episodes of elevated blood pressure during dialysis sessions, which typically normalized following treatment. In the days leading up to his emergency presentation, the patient reported a progressive decline in his health. He felt increasingly fatigued and dizzy, and he experienced episodes of palpitations and shortness of breath during exertion. Excessive sweating accompanied these symptoms, causing significant discomfort. Notably, he reported numbness and tingling in his extremities, indicative of possible hypocalcemia. Family history was significant, revealing that his younger brother had been diagnosed with Bartter Syndrome at just seven months of age, raising suspicions of a genetic predisposition in this case. **Upon admission**, initial laboratory investigations revealed severe electrolyte imbalances that warranted immediate attention. The serum potassium level was critically low at 2.1 mmol/L, and serum calcium was found to be 7.4 mg/dL, both of which are life-threatening. The serum magnesium level was 0.8 mg/dL and the albumin level was 40.2 g/L. The patient exhibited metabolic alkalosis, with a serum bicarbonate level recorded at 32 mmol/L. Renal function tests demonstrated significant impairment, with a creatinine level of 1000 μmol/L, reflecting the severity of his underlying condition. Urine electrolyte analysis showed urinary potassium at 60 mmol/day and chloride at 70 mmol/day, consistent with renal potassium and chloride wasting typical of Bartter Syndrome (see Table 1). A renal ultrasound performed during the admission revealed no structural abnormalities, which helped to rule out obstructive causes for his renal impairment. Common secondary causes of CKD were excluded based on clinical history, imaging, and laboratory workup. Given the patient's neurological and musculoskeletal symptoms, a **magnetic resonance imaging**)MRI(of the lumbar spine was performed (see Figure 2). In addition, due to the patient's family history and clinical findings, genetic testing was conducted. This revealed mutations in the **CLCNKB gene**, which encodes a chloride channel known as chloride channel, voltage-sensitive, KB type. This channel plays a crucial role in regulating the movement of chloride ions across the cell membrane in the kidneys, ensuring proper electrolyte balance. The CLCNKB gene is located on chromosome 1p36, and the resulting protein is identified as P51448. These findings confirmed the diagnosis of Bartter Syndrome Type 3. Management in the hospital was critically focused on correcting the significant electrolyte imbalances. Intravenous potassium and calcium supplementation were promptly initiated, effectively normalizing serum levels and resolving the patient's seizures, thereby preventing further neurological complications. Continuous dialysis was maintained to manage his fluid balance and blood pressure effectively.

Nutritional support played a vital role in his management; a diet rich in potassium and sodium was introduced to help compensate for ongoing renal losses.

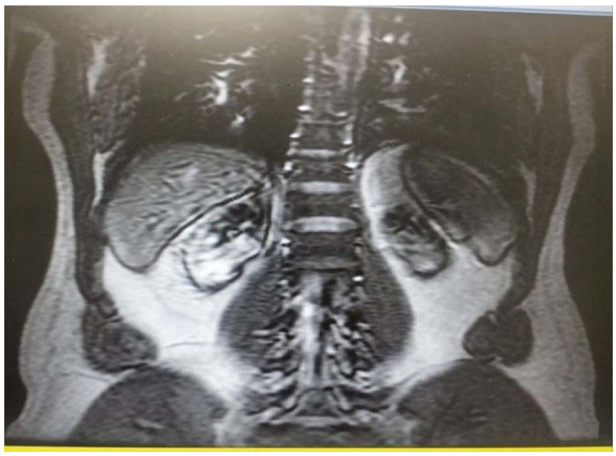

Figure 1. Renal MRI. Bilateral renal atrophy with kidney size asymmetry, where one kidney is larger than the other, indicates chronic kidney disease. This is likely a consequence of long-standing electrolyte imbalances associated with Bartter Syndrome.

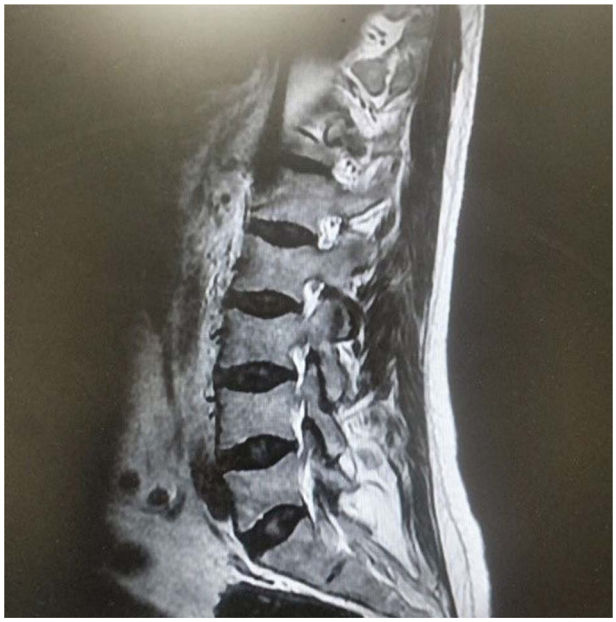

Figure 2. Lumbar spine MRI. As seen in the axial and sagittal views, the MRI demonstrates degenerative changes in the lumbar spine, including intervertebral disc desiccation and mild disc protrusions at **L4-L5 and L5-S1**. There is no evidence of significant spinal cord compression.

Patient education was integral to his management plan. The patient was followed regularly for **eight months** post-discharge, with continued dialysis and supportive care. He showed marked clinical improvement with no recurrence of seizures or electrolyte imbalance. Renal parameters remained stable, and no additional complications were recorded. This favorable response underscores the effectiveness of the multidisciplinary management plan and the importance of regular follow-up.

Discussion

In a previously published paper, after reviewing cases reported between April 2012 and April 2022, a total of 118 patients diagnosed with Bartter syndrome were analyzed. These cases were distributed across 48 case reports and 9 case series, comprising a total of 70 patients. The results showed that the

Table 1. Summary of laboratory results and reference ranges in our patient with Bartter Syndrome type III upon admission.

Test	Patient's Value	Reference Range
Serum Potassium	**2.1 mmol/L**	**3.5–5.0 mmol/L**
Serum Calcium	**7.4 mg/dL**	**8.5–10.2 mg/dL**
Serum Magnesium	**0.8 mg/dL**	**1.7–2.3 mg/dL**
Serum Albumin	**40.2 g/L**	**34–55 g/L**
Serum Bicarbonate	**32 mmol/L**	**22–28 mmol/L**
Serum Creatinine	**1000 μmol/L**	**53–106 μmol/L**
Urinary Potassium	**60 mmol/day**	**25-100 mmol/day**
Urinary Chloride	**70 mmol/day**	**110-250 mmol/day**

Table 2. Summary of clinical and genetic characteristics of different types of Bartter Syndrome from medical literature.

Case Number	Patient Age	Patient Gender	Primary Diagnosis	Responsible Gene	Main Electrolyte Abnormalities	Treatment	Reference
1	21 months	Male	Bartter Syndrome Type I	SLC12A1	Hypokalemia, Hypercalciuria	Indomethacin	[18]
2	26 years	Male	Bartter Syndrome Type II	KCNJ1	Hypokalemia	Potassium supplement, Aldosterone antagonist	[19]
3	22 years	Female	Bartter Syndrome Type III	CLCNKA	Hypokalemia	No specific treatment mentioned	[20]
4	Fetal (preterm, birth at 33 weeks)	Female	Bartter Syndrome Type IVa	BSND	Elevated amniotic fluid chloride levels, polyuria	Indomethacin, nasogastric feeds, intravenous fluids	[21]
5	Newborn	Male	Bartter Syndrome Type V	MAGED2	Hyponatremia, Hypokalemia, Hypochloremia, Hypercalciuria	Parenteral nutrition, KCl, Spironolactone	[22]

majority of patients were male (68), while 50 were female. Additionally, 21 patients were born to consanguineous parents. Regarding geographical distribution, most cases were reported from Asia (73.72%), followed by Europe (15.25%), with the remaining cases originating from other regions worldwide [5].

Defective salt reabsorption in the thick ascending limb (TAL) of the loop of Henle (LOH) leads to Bartter Syndrome (BS). BS is associated with mutations in LOH, causing disturbances in vital laboratory values like hypocalcemia, hypokalemia, hypomagnesemia, and hyponatremia [6]. A previous study suggested that prostaglandins E2 play a crucial role in affecting and causing chloride transport defects in the TAL of Henle [7]. BS has various differential diagnoses including Gitelman syndrome, cystic fibrosis, diuretic abuse, and pyloric stenosis [8]. BS is classified into antenatal Bartter Syndrome (aBS) and classic Bartter Syndrome (CBS), with various patterns, each having specific age groups, symptoms, severity, and characteristics. For instance, aBS involves several symptoms around birth such as polyhydramnios, intrauterine growth retardation, prematurity, and fetal polyuria. The genes affected by aBS are diverse, with SLC12A1 (type I), KCNJ1 (type II), and BSND (type IVa), while CLCNKA and CLCNKB are responsible for type IVb. Type IV is closely associated with hearing loss in patients with this syndrome [9]. Recently, mutations in MAGED2 were also identified, causing a new type of BS known as transient antenatal Bartter Syndrome linked to the X chromosome [10] (see Table 2). Type III, considered the most common BS according to several studies. A previous study on 54 Korean patients confirmed this, aligning with studies from the UK and Japan but differing from others in Germany and France, indicating the need for more research as the prevalence of genetic mutations can vary by country [11]. Mutations in the CLCNKB gene responsible for encoding ClC_kb contribute to the emergence of type III syndrome and its symptoms in adults, as seen in our patient [12]. Although BS patients rarely reach dialysis stage, our patient required regular dialysis due to a history of CKD concurrent with BS. The presence of hyperplasia in the juxtaglomerular apparatus can be present or absent, indicating that kidney biopsy does not play a significant role in diagnosing BS [13]. On the other hand, Liu et al. documented a case of a Chinese boy diagnosed with both BS and CKD, whose kidney biopsy revealed complex juxtaglomerular apparatus hyperplasia [12]. Unlike the referenced case, in a previous study, the infant girl did not progress to dialysis, and no hyperplasia was observed. This indicates that the severity of Bartter Syndrome and its progression to CKD can vary between cases, and that reaching the stage of dialysis is not common in all patients [14]. BS treatment aims to reduce aldosterone and prostaglandin production as much as possible. Additionally, treatment should include potassium supplements to avoid dehydration and hypovolemia, especially in younger patients, with aldosterone antagonists and potassium-sparing diuretics like spironolactone. In Zhou et al.'s report, a few-days-old female patient was treated with blue light to reduce

jaundice and followed up for 22 months with indomethacin and potassium chloride supplements for type III BS diagnosed since the early days of life [15]. Nephrologists and researchers recommend regular follow-up for patients every 6-12 months during adulthood and every 3-6 months in infancy and childhood, along with regular kidney ultrasounds every 12-24 months [16]. For end-stage renal disease (ESRD) patients, particularly those with BS, a kidney transplant is the final solution, with no recurrence of BS after the procedure, as reported by Lee et al. [17]. In our case, our treatment plan for our patient included intravenous potassium and calcium replacement, in addition to nutritional support rich in potassium and sodium, along with educating him about his disease and its long-term consequences and complications.

The limitations of our study were that it described only a single case, which limits the ability to generalize the findings. In addition, the follow-up period was relatively short, and no kidney biopsy or functional studies of the mutations detected in the CLCNKB gene were performed. Furthermore, the report did not adequately address the nutritional and psychosocial aspects in the long term.

In conclusion, this rare case highlights the diagnostic and therapeutic challenges of Bartter Syndrome, particularly type III. The patient showed a good response to continuous treatment and regular follow-up, reflecting the importance of comprehensive medical care. This case underscores the need for further studies to understand the diversity of genetic mutations and their impact on clinical expression. Psychological and social support for patients is essential to improve their long-term quality of life. Collaboration between doctors and researchers should continue to find new and effective ways to treat this rare syndrome.

Authors' contributions

H.H., Y.A., M.M.A., N.M.G., M.S.A., and B.A., wrote the main manuscript text. Dr. Hamdah Hanifa conceived and supervised the conduct of the study. All authors critically reviewed and revised the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Competing interests

The authors declare no competing interests.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Ethics approval and consent to participate

Not applicable.

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