RESEARCH LETTER

Renal artery embolization in an adult patient with Bartter syndrome: a difficult but life-saving decision

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Introduction Bartter syndrome (BS) is a heterogenous group of rare, inherited salt-losing tubular disorders characterized by disturbances in transport mechanisms within the thick ascending limb of the loop of Henle. Data on frequency of BS are scarce, with prevalence reported as 1 per 1 000 000 live births.[1,2] Based on molecular genetics, 5 different forms of BS (BS 1–5) have been distinguished, each correlating with a different phenotype (Supplementary material, *Table S1*). Regardless of the underlying molecular defect, the pathophysiologic basis is sodium reabsorption impairment, which leads to hypovolemia and consequently abnormal activation of the renin-angiotensin system and development of normotensive hyperreninemic hyperaldosteronism with normal/low blood pressure.[2,3] Hypersecretion of prostaglandin E2 and stimulation of the renin-angiotensin system result in chronic glomerular hyperfiltration.[4-6] Most of the described BS cases relate to the pediatric population, as the disease is extremely rarely diagnosed in adults.[6] Despite increasing understanding of the BS pathophysiology, its therapy remains mostly supportive. The main focus of treatment is lifelong electrolyte supplementation and nutritional support. It may be accompanied by prostaglandin E2 suppression through nonsteroidal anti-inflammatory drugs (NSAIDs).[1,3]

The course of the disease is individual and symptoms can range from mild to severe and life-threatening. Clinical findings include polyuria, hypovolemia, salt craving, growth retardation, vomiting, fever, fatigue, dizziness, muscle cramps, nephrocalcinosis, or kidney stones. Prenatal findings include polyhydramnios, intrauterine growth retardation, and premature delivery. In some individuals who experience significant electrolyte imbalances, severe complications, such as irregular heartbeats (cardiac arrhythmias) or muscle weakness may develop.[1,6]

In most patients with BS, the renal function remains well preserved and they do not develop chronic kidney disease (CKD). The exact mechanism behind the CKD development in the course of BS remains unknown, and its etiology is believed to be multifactorial.[7,8]

We present a case of a woman with type 3 BS, who developed severe electrolyte complications and malnutrition, cardiac arrhythmias, and muscle paralysis, and in whom we had to perform renal artery embolization followed by hemodialysis and kidney transplantation.

Patient and methods A 35-year-old woman, with no remarkable medical history, was admitted to a hospital due to recurrent syncope and vomiting. Laboratory tests showed significant electrolyte disturbances in the form of hypokalemia with hyponatremia and hypochloremia. After successful electrolyte supplementation, the patient was discharged home with a recommendation for oral potassium supplementation. One week later she was admitted to a nephrology department presenting with severe dehydration, hypovolemia, hypotension, and consequently acute kidney injury, hyponatremia, hypochloremia, and hypokalemia. The patient did not complain of any hearing impairment, nor was it revealed during physical examination, therefore a hearing test was not performed. Further diagnostics revealed highly elevated plasma renin activity and high aldosterone level. Repeated 24-hour urine collections confirmed excessive daily excretion of sodium, potassium, magnesium, and calcium, but no proteinuria was detected (Supplementary material,

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Received: March 7, 2024.
Revision accepted: April 3, 2024.
Published online: April 4, 2024.
Pol Arch Intern Med. 2024; 134 (4): 16720
doi:10.20452/pamw.16720

Table S2). No abnormalities were found during diagnostics for potential autoimmune diseases, which included tests for the presence of antinuclear antibodies, antineutrophil cytoplasmic antibodies, anti–double-stranded DNA antibodies, and lupus anticoagulant. Erythrocyte sedimentation rate as well as serum levels of ferritin and C3 and C4 complement were within a normal range. A number of cancer screening procedures, including abdominal ultrasound, chest X-ray, serum biomarkers for ovarian and breast cancer, gastroscopy, colonoscopy, and bone marrow biopsy were performed, revealing only chronic gastritis. After electrolyte and water balance were restored with intravenous fluids, kidney function returned to normal. A clinical diagnosis of BS was established, and genetic tests revealed a mutation in the *CLCNKB* gene, confirming the diagnosis of type 3 BS. Within the following 3 years, the patient's general condition and kidney function were slowly deteriorating and the patient required a gradual increase of electrolyte supplement doses, as well as implementation of aldosterone antagonist agent to ameliorate the electrolyte abnormalities and mitigate their symptoms, which were still present despite optimization of routine treatment and full patient's compliance with the therapy. NSAIDs could not be implemented due to symptomatic gastritis not responding to gastric acid suppression. The patient was constantly presenting with exacerbation of muscle weakness, fatigue, vomiting, and consequent dehydration, and had to be referred multiple times to our center for intravenous restoration of electrolyte balance. Three years after the diagnosis, the symptoms and the laboratory parameters could no longer be effectively managed with oral treatment. Therefore, a vascular port was inserted and intravenous electrolyte supplementation at home was implemented. Despite conducting both oral and intravenous treatment at maximum tolerated doses at home, a gradual decrease in glomerular filtration rate, refractory electrolyte abnormalities, and aggravation of signs and symptoms were observed in the following 6 years. Additionally, the patient required several hospitalizations due to vascular port–related bacteremia with concomitant severe electrolyte disbalance, dehydration, and recurrent acute kidney injury (AKI). Altogether, over 6 years after the first vascular port insertion, the patient experienced 7 episodes of AKI related to dehydration and hypotension, and the vascular port had to be reimplanted 7 times due to its dysfunction or bacteremia. As a consequence, the patient developed major occlusions of deep veins of the upper body resulting in abundant formation of collateral circulation. This made implantation of another vascular port or creation of a vascular access for hemodialysis highly challenging. In the course of recurrent staphylococcal septic episodes, the patient eventually developed multiple pulmonary abscesses and acute diffuse peritonitis, for which she had to undergo emergency laparotomy. Major abdominal surgery resulted in formation of multiple peritoneal adhesions, leading to chronic abdominal pain, recurrent intestinal obstructions, and obstructive liver and pancreas insufficiency. By the age of 44 the patient was cachectic, in chronic pain, unable to walk, bedbound, and dependent on others. The only chance for the patient was to stop the excessive loss of electrolytes with urine. After thorough consideration, a joint decision of unilateral functional nephrectomy as a last-chance treatment was made. A dynamic renal scintigraphy using ^{99m}Tc-ethylenedicysteine was performed, revealing delayed excretion of the radiopharmaceutical by the right kidney, with partial response after the diuretic test (with furosemide administered intravenously 20 minutes after the radiopharmaceutical, according to F+20 protocol[9]). Right and left kidney were responsible for the excretion of 33% and 67% of the administered radiopharmaceutical, respectively. Apart from relative renal function, kidney efficiency index (KEi) was also assessed. Its values were 7.46 for the right kidney and 9.82 for the left kidney (normal range, KEi >8)[10] (**FIGURE 1**). As the left kidney showed better performance, it was selected for an elective nephrectomy. However, cachexia and very poor general condition of the patient posed a very high risk of perioperative complications, and therefore classic nephrectomy was abandoned. We decided to follow a less invasive procedure, namely embolization of the renal artery. A pre-emptive implantation of a permanent hemodialysis catheter using the right femoral vein was performed. Total left renal artery embolization with coil deployment was performed. With a gradual but profound decrease of daily diuresis and kidney function loss, the patient reached end-stage kidney disease (ESKD) within a few days after the procedure, and had to start chronic hemodialysis at the age of 44, nearly 9 years after the onset of symptoms and establishing the diagnosis of BS. A progressive improvement of the patient's clinical condition, nutrition, and water-electrolyte imbalance was observed, which allowed us to qualify her for kidney transplantation.

Ethics This study was conducted in accordance with the Declaration of Helsinki. As this is a retrospective study avoiding any information revealing the patient's identity, ethics approval is not applicable. Written informed consent for publication of the data and images have been given by the patient. Further data regarding this study are available from the corresponding author upon reasonable request.

Results Three weeks after placing her on a waiting list, 17 months after starting hemodialysis, and slightly over 10 years after establishing the diagnosis of BS, the patient underwent kidney transplantation from a deceased donor. Within the next 3 weeks, a gradual increase in daily diuresis was seen, with no serum electrolyte disturbances (Supplementary material, *Table S3*).

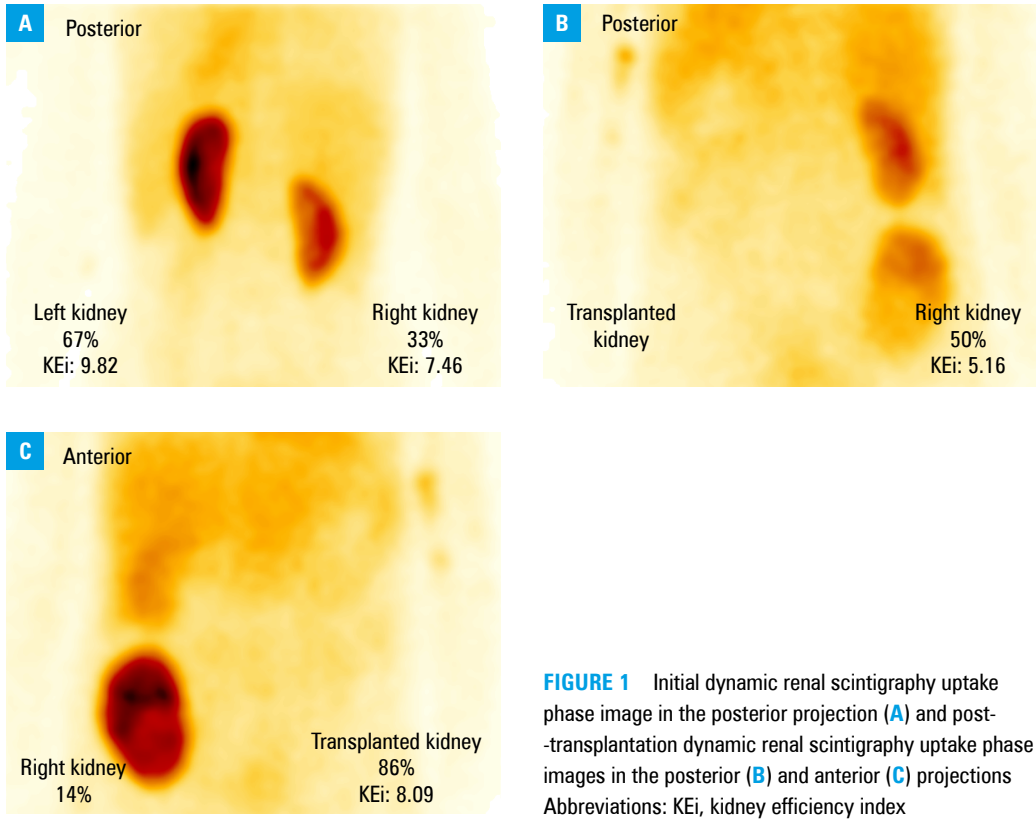

FIGURE 1 Initial dynamic renal scintigraphy uptake phase image in the posterior projection (**A**) and post-transplantation dynamic renal scintigraphy uptake phase images in the posterior (**B**) and anterior (**C**) projections
Abbreviations: KEi, kidney efficiency index

Post-transplant dynamic renal scintigraphy confirmed good kidney graft function. The relative function of the native right kidney and transplanted kidney, calculated as a mean from the posterior (P) and anterior (A) projection, was 32% (PA, 50%; AP, 14%) and 68% (PA, 50%; AP, 86%), respectively, and the native left kidney remained inactive since renal artery embolization. KEi, which represents kidney function in absolute values, revealed a decline in the right kidney function (with a value of 5.16), and normal function of the transplanted kidney (KEi, 8.09; assessed in the anterior projection) (FIGURE 1). The patient required neither hemodialysis, nor electrolyte supplementation.

Six months after the renal transplantation and intensive physical rehabilitation, the patient was able to carry out normal everyday activities and returned to work.

Discussion Our patient was diagnosed based on genetic tests at the age of 35, due to oligosymptomatic course of the disease. Type 3 BS is caused by mutations in the *CLCNKB* gene, encoding a kidney-specific basolateral chloride channel. Type 3 BS is usually diagnosed in early childhood, mostly at school age, and it is very uncommon to present with BS in adulthood.

Due to poor response to pharmacotherapy, the patient's kidney function gradually deteriorated, and 9 years after diagnosis her estimated glomerular filtration rate reached 40 ml/min/1.73 m^2 (CKD stage 3b). The patient had no history of NSAID overuse, nor of nephrocalcinosis. Although renal biopsy was not performed, focal segmental glomerular sclerosis could be ruled out due to a lack of proteinuria in repeated urine collections. This suggested that the recurrent episodes of hypovolemia and hypotension were the most probable causes of renal impairment. In a relatively large cohort of patients with *CLCNKB* mutations, CKD was reported in 19 out of 77 individuals (25%), with 10 of them presenting stage 2 CKD, 2 stage 3 CKD, 1 stage 4 CKD, and 6 stage 5 CKD. The median (interquartile range) follow-up was 8 (1–41) years.[11]

Due to severe electrolyte disturbances, deteriorating general condition of the patient, which made it impossible for her to function independently, despite a lack of end-stage renal failure, a decision was made to perform iatrogenic nephrectomy in order to stop the loss of electrolytes with urine. Case reports of patients with BS undergoing renal transplantation are rare.[5,12-14] Most of them described patients who developed glomerulopathies in the course of BS with subsequent ESKD. One case report described kidney transplantation in a patient who developed ESKD due to excessive NSAID use.[13] Only 2 cases of pre-emptive native nephrectomy and consequent successful renal transplantation have been reported.[14] Both of them involved children with severe neonatal BS, and both nephrectomies were performed due to refractory electrolyte and fluid loss resulting in failure to thrive.

In order to assess kidney function, both before the planned embolization and after kidney transplantation, we performed dynamic renal scintigraphy. Apart from relative renal function, KEi, a parameter proportional to kidney clearance

function, was also assessed. The relative function of the native right kidney calculated as mean of the posterior and anterior projection was similar to the examination before embolization. This parameter was not reliable in that clinical situation, since it is relative to the other kidney (now replaced by the transplanted kidney). KEi, which represents kidney function in absolute values, revealed a decline in the right kidney function.

We found out that pre-emptive nephrectomy with subsequent renal transplantation in an adult patient with BS resulted in complete correction of electrolyte abnormalities, nutritional status, and improved quality of life allowing the patient to return to proper functioning in everyday life.

This case also highlights the limitations of assessing relative renal function using dynamic renal scintigraphy and the importance of using other parameters, such as KEi, to assess renal function in absolute values, which is essential for further follow-up studies in patients after nephrectomy or kidney transplantation.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS None.

FUNDING Open access funding provided by the Medical University of Lodz, statutory grant number 503/1-151-02/503-11-001-18.

CONFLICT OF INTEREST None declared.

HOW TO CITE Kieszek B, Cichocki P, Adamczewski Z, et al. Renal artery embolization in an adult patient with Bartter syndrome: a difficult but life-saving decision. Pol Arch Intern Med. 2024; 134: 16720. doi:10.20452/pamw.16720.

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