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Case Report

BRASH Syndrome: A Rare Clinical Phenomenon

Nicholas Roma, MD,[a] Vikram Padala, BS,[b] Megan Pattoli, DO,[a] Spandan Desai, MD,[a] Matthew Krinock, DO,[c] Matthew Durkin, MD,[c] Patrick Field, MD,[c] and Tarick Sheikh, MD[c]

[a] *Department of Internal Medicine, St. Luke's University Health Network, Bethlehem, Pennsylvania, USA*

[b] *Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA*

[c] *Department of Cardiology, St. Luke's University Health Network, Bethlehem, Pennsylvania, USA*

Bradycardia, renal failure, atrioventricular nodal blockade, shock, and hyperkalemia (BRASH) syndrome is a rare medical phenomenon, with only approximately 70 reported cases, carrying a mortality of 5.7%.[1,2] Presentation is variable, but it can range from asymptomatic bradycardia to multisystem organ failure.[3] The unique pathophysiology of BRASH syndrome involves synergy between atrioventricular nodal blocking agents and hyperkalemia, leading to severe bradycardia and renal malperfusion. Here, we present a case of a 66-year-old female patient who was found to fit the clinical picture of BRASH syndrome, in whom the prompt diagnosis and intervention led to a positive outcome.

Case Report

A 66-year-old female patient presented with a chief complaint of fatigue and was found unresponsive by her son, who reported her having been obtunded and incontinent earlier that day. However, prior to that day, she was functioning well and hydrating adequately. The patient has a complex medical history, with the most pertinent including heart failure with preserved ejection fraction, moderate aortic stenosis, permanent atrial fibrillation, and chronic kidney disease 3a. The patient was being treated medically with apixaban 5 mg twice daily, diltiazem extended-release 360 mg once a day, and metoprolol tartrate 50 mg twice daily. A transthoracic echocardiogram obtained 3 months prior revealed a left ventricular ejection fraction of 50%, a severely dilated left atrium, severely calcified aortic leaflets with moderate-to-severe stenosis, mild-to-moderate mitral regurgitation, and moderate tricuspid regurgitation. The patient also had been prescribed potassium chloride 10 mEq daily for hypokalemia, and furosemide 40 mg twice daily for peripheral edema.

En route to the emergency department (ED), the patient was found to be in third-degree heart block with a heart rate of 20 beats per minute (bpm), prompting emergency medical services to begin transcutaneous pacing (rate 80, current of 80 mA). In the ED, epinephrine 2 mcg/min was given, and transcutaneous pacing (rate 80, current 200 mA) was continued. (Fig. 1) Epinephrine was raised to 4 mcg/min, and transvenous pacing through her right internal jugular vein was started, greatly improving the patient's mental status. The patient's vital signs were stable at this time. Her lab tests were notable for hyperkalemia (8.1 mmol/L), so she was given calcium, insulin, glucose, and albuterol. The patient also was found to have an elevated creatinine level (221 μmol/L). A computed tomography scan of the abdomen was performed, showing no acute findings. Epinephrine was able to be weaned off 2 hours after her arrival to the ED. Transvenous pacing was stopped temporarily before being restarted due to 2, brief episodes of asystole while it was paused. The following day, her potassium level was reduced to 5.2 mmol/L, and she no longer required pacing with a heart rate of 70 bpm, although she had atrial fibrillation with narrow QRS complexes. Over the next 24-hour period, the patient had heart rates ranging from 100 to 130 bpm; however, no pharmacologic intervention occurred. The patient's other vital signs, including blood pressure, were within normal limits during this time. Upon review of prior electrocardiograms, she was diagnosed with tachy-brady syndrome and was scheduled for placement of a leadless pacemaker.

The patient underwent a leadless pacemaker implantation without complications. An LSP112V AVEIR (Abott, Los Angeles, CA) leadless pacemaker was used, owing to its utility in cases of bradycardia and irregular heart rhythms, both of which were seen in this patient. The pacemaker was set to a VVI setting, with a backup rate of 60 bpm, and chest x-ray confirmed stable right ventricular placement. On discharge, her potassium level (3.9 mmol/L) and creatinine level (102 μmol/L) normalized. She was scheduled for a follow-up and was slowly started on metoprolol succinate extended-release

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Corresponding author: Dr Nicholas Roma, St. Luke's University Health Network, 801 Ostrum Street, Bethlehem, Pennsylvania 18015, USA. Tel./fax: +1-484-526-4644.

E-mail: nroma127@gmail.com

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Novel Teaching Points

- The prompt identification and treatment of BRASH syndrome can lead to better patient outcomes.
- BRASH syndrome mimics many other common etiologies seen by hospitalists and emergency room physicians; thus, being able to distinguish BRASH syndrome is a skillset.
- BRASH syndrome is a clinical diagnosis defined by the cycle of bradycardia → renal impairment → hyperkalemia → bradycardia.
- BRASH syndrome should be managed by simultaneously treating bradycardia with inotropes and/or chronotropes, treating hyperkalemia with kaluresis or agents that shift potassium intracellularly, and varying fluid status with the necessary intervention.
- Although the goal of treatment is stabilization of the patient through minimally invasive measures, our case highlights the importance of evaluating the patient for future arrhythmias and the benefits of permanent pacemaker implantation in these cases.

75 mg once a day, and diltiazem 240 mg once a day. At the follow-up, the patient had no complaints. Additionally, her device's parameters were all within normal limits and showed no significant high-rate episodes.

Discussion

The patient's complex medical history includes over 5 comorbidities, a finding seen in 14.3% of patients with bradycardia, renal failure, atrioventricular (AV) nodal blockade, shock, and hyperkalemia (BRASH) syndrome.[2] Among these reported cases, 18.6% were taking a combination of nondihydropyridine calcium-channel blockers (CCBs) and beta-blockers.[2] Bradycardia in these patients can present superimposed on a variety of arrhythmias, including junctional escape rhythm (50%), sinus bradycardia (17.1%), and complete heart block (12.9%).[2] Hyperkalemia severity can vary. This patient's hyperkalemia may have been multifactorial due to chronic kidney disease, diabetes, and potassium supplementation. Our patient presented with bradycardia in the setting of complete heart block, severe hyperkalemia, and a medication list that included diltiazem (nondihydropyridine CCB) extended-release 360 mg once a day, and metoprolol tartrate (beta-blocker) 50 mg twice daily.

The cycle that defines BRASH syndrome includes bradycardia, which can lead to renal malperfusion, acute kidney injury, and thus hyperkalemia. This hyperkalemia then can worsen bradycardia in these patients, which will decrease renal perfusion further, completing the cycle. This cycle usually is initiated by severe AV nodal blockade or acute kidney injury, and patients can continue to deteriorate into multiorgan failure without proper intervention. The exact trigger for this patient is unclear. Both hyperkalemia and heart block are plausible triggers. The severe hyperkalemia could have been caused by the overuse of the patient's potassium supplements or an acute kidney injury caused by her nitrofurantoin. Heart block could have been caused by the concurrent use of beta-blockers and CCBs. The Naranjo Adverse Drug Reaction Probability Scale provided a score of 6 when used to evaluate the relationship between the patient's heart block and CCBs and beta-blockers, meaning that these medications were a "probable" cause of heart block in this patient.[4] Although the trigger was not known, the clinical cyclic syndrome of BRASH was still present. Although most patients presenting

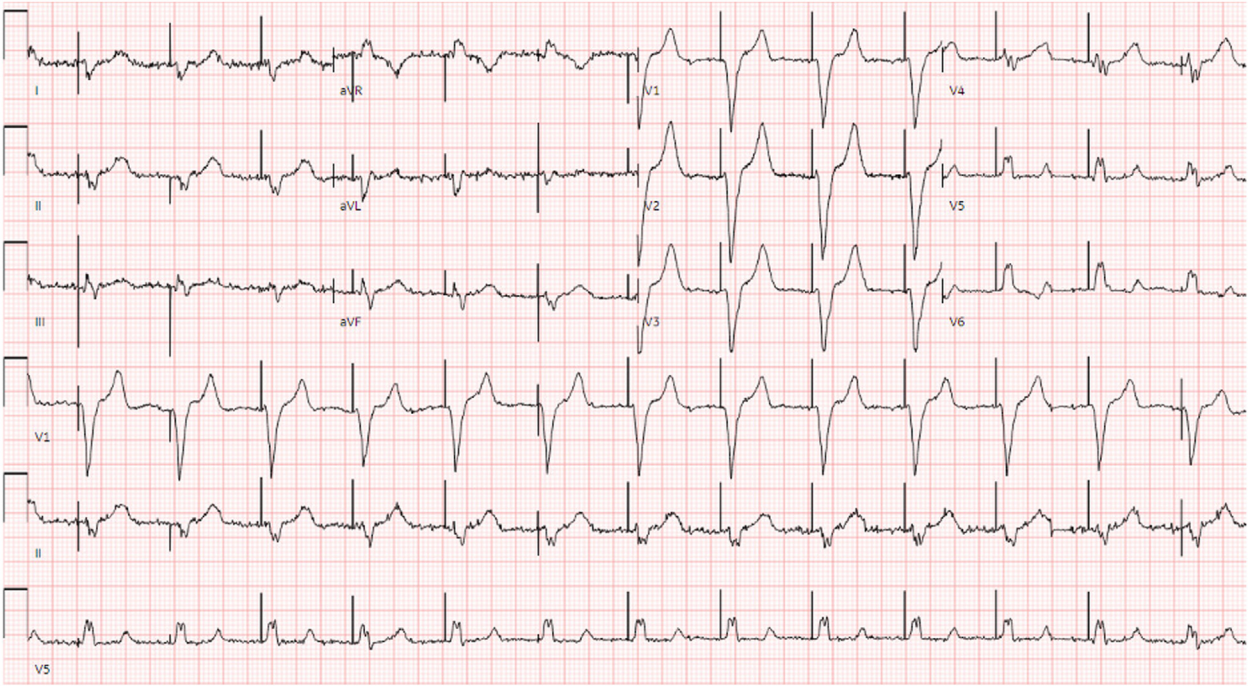

Figure 1. Transcutaneously paced rhythm of patient.

with this clinical syndrome have favourable outcomes with minimally invasive treatment, they have the potential to rapidly progress to multiorgan failure, with a 5.7% mortality rate.[2]

Treatment requires addressing the various parts of this cycle simultaneously. Bradycardia can be managed using positive inotropic and chronotropic agents (epinephrine, isoproterenol, etc.). In regard to hyperkalemia, intravenous calcium (calcium gluconate or calcium chloride), insulin, and dextrose should be given to stabilize the myocardium and move potassium into the cell. In addition, our patient was given nebulized albuterol to promote rapid intracellular shift of potassium, but its use has never been reported in other reported cases of BRASH. If the hyperkalemia persists, kaliuresis with potassium-wasting diuretics, and fluid resuscitation using Ringer's lactate, in addition to potassium binders, should be explored. This patient did not require these treatments. Additionally, upon correction of the hyperkalemia, the patient's AV conduction initially did improve, favouring BRASH syndrome. Fluid status can vary in these patients, as hypovolemia can be a contributing factor to the onset of this syndrome, but renal failure can lead to fluid overload.[1] Additional interventions needed in severe cases include transvenous pacing to maintain perfusion, dialysis for kidney failure, and reversal agents such as lipid emulsion, glucagon, and high-dose insulin infusion in the case of beta-blocker or CCB toxicity.[1]

BRASH syndrome patients (~32.9%) typically require transvenous or transcutaneous pacing, with no patients having undergone placement of a permanent pacemaker.[2] Our patient showed a high propensity for tachycardia and bradycardia, which would only worsen after the necessary reinitiation of AV nodal blocking agents for her atrial fibrillation. Due to the multiple failed trials of rate control during her initial hospitalization, permanent pacemaker implantation was recommended. Leadless pacemaker placement was chosen out of operator preference.

Currently, no data have been gathered regarding restarting AV nodal blocking agents after BRASH syndrome. Literature review suggests a shared decision-making conversation between providers and patients regarding the risks and benefits in restarting beta-blocker or non-dihydropyridine CCB therapy.[5,6] This patient's home regimen AV nodal blocking agent therapy of metoprolol and diltiazem resumed after pacemaker placement. This treatment was considered appropriate considering the significant difficulty in rate control of atrial fibrillation noted in her past medical history, as well as stabilization of electrolytes and improvement in kidney function. The patient's heart rates were controlled through the remainder of her hospitalization. At a 2-week device check and follow-up, the patient's vital signs were within normal limits, and her device interrogation showed no significant high-rate episodes.

Although the development of other arrhythmias is not reported extensively in cases of BRASH syndrome, this patient shows that the development of BRASH syndrome may indicate a propensity for irregular heart rhythms. Thus, evaluation for other irregular heart rhythms should be conducted in these patients, and placement of permanent pacemakers should be considered. This case reminds us of how BRASH syndrome can be identified and managed.

Ethics Statement

This research has adhered to the relevant ethical guidelines.

Patient Consent

The authors confirm that a patient consent form has been obtained for this article.

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Disclosures

The authors have no conflicts of interest to disclose.

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