BRASH syndrome: More than just syncope

Divya Vangipuram MD, Kenneth Nugent MD

ABSTRACT

The pentad of bradycardia, renal failure, atrioventricular nodal blockade, shock, and hyperkalemia describes the BRASH syndrome, a newly recognized phenomenon in which accumulation of potassium and renally excreted atrioventricular nodal blockers cause a cycle of bradycardia, hypoperfusion, and worsening renal function. Here, we describe a case of BRASH in an elderly woman whose medications had recently changed, and who presented with bradycardia, anuria, and hypotension. Resolution of symptoms occurred over hours after the correct treatment was started. Furthermore, we review case reports written in recent years for common BRASH syndrome patient characteristics.

Keywords: Bradycardia, hyperkalemia, shock, AV nodal blocker, critical care

INTRODUCTION

BRASH syndrome–bradycardia, renal failure, atrioventricular (AV) nodal blockade, shock, and hyperkalemia–is a newly described clinical disorder first detailed in 2012[1] and recognized in 2016.[2] It is most often seen in the emergency medicine and critical care settings in elderly patients with cardiac conditions managed with AV nodal blocking agents, underlying kidney disease, and a cause for hypoperfusion. A cycle of worsening kidney function, hyperkalemia, medication accumulation, and bradycardia develops quickly and can progress to multi-organ dysfunction if untreated.[2]

CASE PRESENTATION

A 75-year-old Caucasian woman with hypertension, hyperlipidemia, type II diabetes mellitus, history of first-degree AV block, and coronary artery disease with two stents placed in 2012 had a witnessed syncopal event while sitting in the lobby of a doctor's office.

Corresponding author: **Divya Vangipuram**
Contact Information: D.vangipuram@ttuhsc.edu
DOI: 10.12746/swrccc.v9i40.827

After 10–15 seconds, the patient regained consciousness, was alert and fully oriented, and did not have bowel or bladder incontinence. Paramedics found the patient to have a blood pressure of 70/50 mmHg and a heart rate of 28 beats per minute (BPM). She was given atropine and glucagon in route to the hospital.

In the emergency department, vital signs showed blood pressure of 68/43 mmHg, heart rate of 28 BPM, normal body temperature, and oxygen saturation above 92% on room air. She was placed on a non-rebreather mask for mild tachypnea. She reported 2–3 days of decreased fluid intake, a mild, dull, intermittent left anterior chest pain without radiation and one day of dizziness. Physical examination revealed a groggy but oriented, frail appearing elderly woman with dry oral mucosa, no trauma to the head, clear lung fields bilaterally with mild tachypnea, regularly irregular heart rate without murmur, soft and non-tender abdomen, thready pulses, and cool extremities.

Home medications included subcutaneous insulin, metformin, glimepiride, atorvastatin, aspirin, amitriptyline, amlodipine, furosemide, diltiazem, and metoprolol tartrate. Diltiazem was increased from 240 mg daily to twice a day and metoprolol was decreased from 50 mg twice a day to daily by her cardiologist one week prior to presentation. These doses were changed due to persistent hypertension and borderline bradycardia

with a heart rate of 56 BPM and a blood pressure of 162/63 mmHg at the time of this appointment. She reported strict compliance with all prescribed medications.

Investigations

Work-up in the emergency department showed a normal complete blood count. Metabolic panel was significant for potassium of 6.4 mmol/L without hemolysis, bicarbonate of 14 mmol/L, anion gap of 21, BUN of 35 mg/dL, creatinine of 1.9 mg/dL, eGFR 25 mL/min, and glucose of 471 mg/dL. Serum acetone was negative. Troponin and one-hour repeat level were within normal range. Serum osmolality was high, and lactate was 7.1 mmol/L. Arterial blood gas showed pH 7.136, pCO2 29.6 mmHg, pO2 119.4 mmHg, bicarbonate 9.8 mEq/L, and lactate 4.72 mmol/L, indicating lactic and metabolic acidosis with acute respiratory compensation. Urinalysis showed no infection and mild glucosuria, proteinuria, and ketonuria. Urine electrolytes showed a fractional excretion of sodium of 0.4%, indicating pre-renal azotemia.

The initial electrocardiogram (ECG, Figure 1) showed sinus arrest with ventricular escape rhythm with rate of 28 beats per minute, QRS 129 milliseconds (ms), QTc 381 ms, peaked T waves, and no P waves. Chest x-ray did not show infiltrates, effusion, or cardiomegaly.

Differential diagnosis

As the presentation of BRASH syndrome can vary, the differential diagnosis must be broad. In this case, the differential included hyperkalemia, AV nodal blocker toxicity, infection, hypothyroidism, and cardiac structural, perfusion-related, and conduction abnormalities.

Treatment

For initial resuscitation, the patient was given two doses of 0.5 mg intravenous atropine, 1 mg glucagon, one liter of normal saline, and calcium gluconate and insulin for bradycardia, hypotension, and hyperkalemia respectively. Dextrose was not administered due to hyperglycemia. The patient was started on a dopamine infusion. Over the next 15 minutes, hypotension and bradycardia persisted and the patient began to have altered mentation and increasing drowsiness. Epinephrine infusion was started, and within minutes mentation, blood pressure, and heart rate improved. Dopamine was quickly weaned off after epinephrine was started. The patient remained on the epinephrine infusion for 4 hours.

Due to hyperkalemia, acute kidney injury, and oliguria with 15 mL of urine output over 3 hours spent in the emergency department, nephrology was consulted, central venous access for emergent dialysis was obtained, and hemodialysis was initiated within an hour. However, due to catheter malfunction secondary to clot formation, dialysis was stopped in 17 minutes. Repeat renal function panel was drawn and showed improvement, with potassium at 5.3 mmol/L, creatinine 1.4 mg/dL, and an eGFR of 36 mL/min. The patient was given one dose of 10 mg sodium zirconium cyclosilicate (an oral potassium binder) and observed. Over the next 12 hours, she had 500 mL of urine output.

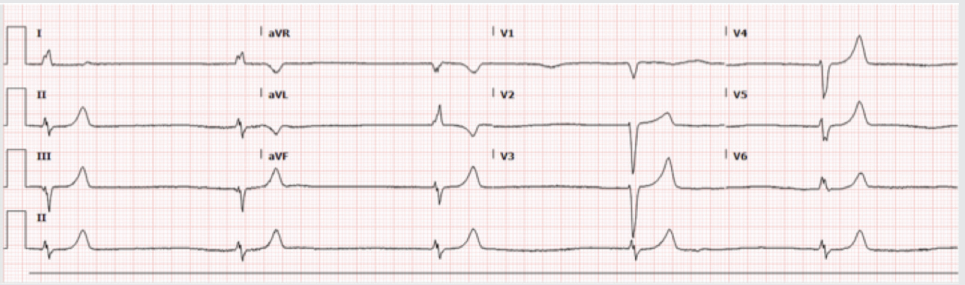

Figure 1. ECG on initial evaluation, which shows junctional rhythm.

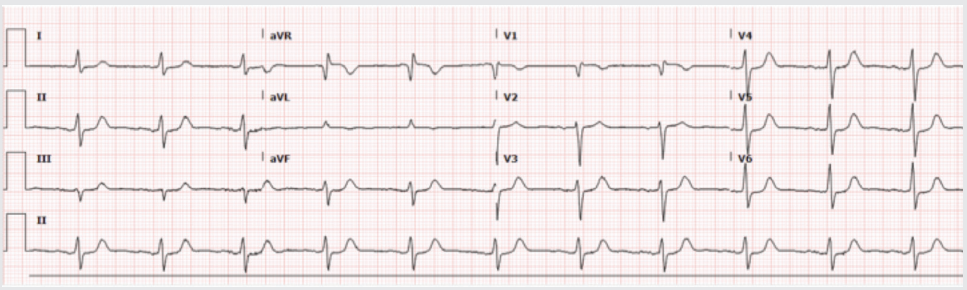

Figure 2. ECG on day of discharge, which shows first degree AV block.

Outcome and follow up

She remained in the hospital for three days, and her overall course was uncomplicated. She spent one night in the intensive care unit as epinephrine was weaned off and was sent to the general ward the next morning. Kidney function continued to improve over the next day. She did not receive dialysis again. Stress test, echocardiogram, and carotid ultrasound were performed and did not reveal mechanical or perfusion defects. An electrocardiogram on the day of discharge showed sinus rhythm with first-degree AV block and left axis deviation (Figure 2), unchanged from prior admissions. On discharge, cardiac medications were revised. Diltiazem and amlodipine were discontinued, 20 mg daily lisinopril was added, and metoprolol tartrate was changed from 50 mg daily to 25 mg BID. She was discharged home on the third day of admission with close follow up with her cardiologist, her primary care physician, and a nephrologist.

At her follow up appointment with the cardiologist, metoprolol was increased to 25 mg in the morning and 50 mg at night. Two weeks later, at her follow up with the primary care physician, she denied new episodes of syncope and a log of heart rate and blood pressure since discharge showed normal, stable vital signs. She was formally diagnosed with CKD III with a baseline creatinine of 1.2 mg/dL at her follow up with nephrology.

Discussion

Both beta-blockers and non-dihydropyridine calcium channel blockers (diltiazem, verapamil) are atrioventricular node blocking drugs and are primarily excreted by the kidneys. The crux of BRASH syndrome lies in the synergistic effect of accumulated levels of medication and potassium in the setting of renal dysfunction due to hypoperfusion. This effect causes bradycardia, which reduces cardiac output, and thus decreases renal perfusion, further worsening kidney injury, and causing a vicious cycle.[2–4]

Work-up should initially be directed toward differentiating between hyperkalemia, AV nodal blocker toxicity, and BRASH syndrome with a thorough clinical history. Patients with bradycardia related to hyperkalemia caused by kidney failure, medications, Addison's disease, diabetes, and hemolytic conditions often have potassium levels above 7 mmol/L and ECG changes, such as peaked T waves and QRS prolongation. Patients with AV nodal blocker toxicity may or may not have hyperkalemia, may report recent changes in cardiac medications, and present in the setting of overdose. BRASH syndrome patients always have hyperkalemia, although levels are often lower than expected given the degree of bradycardia present, and report compliance with medications.[2–4]

Treatment of hyperkalemia, bradycardia, and hypotension should occur concurrently. Hyperkalemia should be addressed immediately, regardless of the degree, and treatment should consist of intravenous calcium to stabilize cardiac myocytes, with insulin, dextrose, and albuterol.[2–5] Definitive treatment of hyperkalemia, acidosis, and kidney injury after initial stabilization is dictated by urine output–if low or none, dialysis should be pursued quickly. If the patient has urine output, alkalization with bicarbonate infusion and kaliuresis with potassium-wasting diuretics with isotonic fluid replacement and potassium binding agents are the preferred therapy.[2–4] Bradycardia should be

Table 1. BRASH Case Series and Reports

Year	Author	Age	Medications	Chief Complaint	HR	K+	Treatment
1986–2019	Farkas[2]	70 (mean, n = 18)	AV nodal blockers, most commonly verapamil	Varied	45	6.8	Varied
2017–2018	Ravioli[5]	80 (mean, n = 8)	Beta blocker	Varied	—	5.8	Fluids, potassium shifting agents, catecholamine infusion
2019	Sohal[6]	89	Diltiazem	Bradycardia, weakness	35	8.6	Dopamine, isoproterenol, calcium, insulin, dextrose, polysterene sulfonate
2019	Gonuguntla[7]	67	Diltiazem, nadolol	Dizziness, weakness, diarrhea	20s	—	Fluids, dopamine infusion
2019	Diribe *et al.*[8]	52	Carvedilol, epleronone, TMP/SMX	Syncope	20	8.6	Calcium, insulin, dextrose, albuterol, diuresis, potassium binder
2020	Liou[9]	55	Diltiazem, metoprolol	Heart failure, atrial flutter	—	—	Glucagon, calcium, insulin, dextrose
2020	Cheung[10]	77	Metoprolol, lisinopril	Vomiting	38	6.4	Atropine, dopamine infusion, calcium
2020	Srivastava[11]	62	Carvedilol	Weakness	30s	8.0	Potassium binders, fluids, dopamine infusion
2020	Golchin[12]	84	Beta blocker	Weakness, polyuria	30s	7.1	Dialysis, dopamine infusion
2020	Prabhu[13]	75	Carvedilol, verapamil	Syncope, hypotension, bradycardia	33	6.5	Dopamine infusion, calcium, insulin, bicarbonate, fluids
2020	Arif[14]	55	Diltiazem	Dyspnea, edema, drowsiness	30s	5.4	Dopamine infusion, dialysis
2020	Grigorov[15]	43	Diltiazem, metoprolol	Lethargy, went into PEA	35	7.6	Fluids, norepinephrine infusion, insulin, dextrose, bicarbonate, calcium, transfer for higher level of care
2020	Barreras[16]	80	Beta-blocker	Found down	33	5.3	ACLS for PEA, expired
2020	Sattar[17]	66	Carvedilol,	Pre-syncope	35	6.2	Fluids, calcium, insulin
2020	Sarvottam[18]	63	Beta-blocker	Generalized weakness	40	9.0	Calcium, insulin, dextrose, albuterol, dialysis
2020	Flores[19]	74	Metoprolol, lisinopril	Anaphylaxis	40	7.1	Epinephrine infusion, calcium, albuterol
2020	Savage[20]	81	Atenolol, ramipril	Stroke	29	8.3	Dialysis, atropine

Table 1. BRASH Case Series and Reports (*Continued*)

Year	Author	Age	Medications	Chief Complaint	HR	K+	Treatment
2020	Nathani[21]	62	Metoprolol, nifedipine	Diarrhea, weakness	38	6.4	Fluid, calcium, insulin, dextrose, albuterol, bicarbonate infusion, atropine
2021	Vishnu[22]	60	Atenolol, amlodipine	Abdominal pain, nausea and vomiting, syncope, dizziness	32	6.2	Calcium, insulin, dextrose, albuterol, bicarbonate push, isoproterenol, dialysis
2021	Wong[23] (case series)	62	Atenolol, diltiazem	Vomiting, diarrhea	40	6.2	Dopamine infusion, insulin, dextrose, calcium, epinephrine
		44	Diltiazem, metoprolol	Dizziness	48	5.5	Dopamine infusion, calcium, insulin, dextrose
2021	Ata[24]	64	Bisprolol, sacubitril/ val-sartan	Fatigue, diarrhea, vomiting, anorexia	28	5.8	Fluids, insulin, dextrose, salbutamol, dialysis; expired
2021	Ahad [25]	63	Metoprolol, losartan	Malaise, dyspnea, vomiting, diarrhea	21	5.9	Atropine, glucagon; fluids, epinephrine infusion, calcium, dextrose, insulin
2021	Gulati [26]	58	Enalapril, amiodarone	Chills, dyspnea	40s	5.2	Fluids, albumin, calcium, bumetanide

HR: heart rate; K+: serum potassium level, in mmol/L.

treated with chronotropic agents, preferably epinephrine, which also can cause intracellular potassium shift.[3] Hypotension should be treated with fluid resuscitation, typically with a balanced crystalloid or isotonic bicarbonate in the setting of acidosis. Caution should be exercised if the patient has underlying congestive heart failure or anuric renal failure, which could precipitate pulmonary edema.[2,3]

A review of literature for "BRASH syndrome" was conducted via PubMed and Google Scholar and revealed 23 publications, including case series and case reports published from 2019 to the present time with a total of 66 patients described (Table 1). The average patient age was 68.1 years old, presented most often with weakness and dizziness, had an average heart rate around 35 beats per minute, and mean serum potassium of 6.6 mmol/L. Of the 66 patients, 65 were on a beta-blocker or calcium channel blocker. One patient's[26] source of AV nodal blockade was due to amiodarone. Two of the 66 patients died.[16,24] In most of the cases reported, a known cause of hypotension was present. Diarrhea and vomiting were most common, and there was one case of anaphylaxis related hypovolemia.[19] However, in two cases, antibiotics and nephrotic syndrome were implicated in the development of BRASH syndrome.[8,26]

Key points

- Consider BRASH syndrome in an elderly patient with cardiac disease treated with an AV nodal blocker, baseline renal dysfunction, and a cause for hypoperfusion.
- If suspected, address metabolic derangements, hypotension, and bradycardia concurrently.
- Use urine output to direct medical therapy for renal failure and hyperkalemia.
- Anticipate reversal of symptoms relatively quickly once identified and treated appropriately.

Article citation: Vangipuram D, Nugent K. BRASH syndrome: More than just syncope. The Southwest Respiratory and Critical Care Chronicles 2021;9(40): 53–59
From: Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, Texas
Submitted: 4/25/2021
Accepted: 6/25/2021
Reviewer: Deephak Swaminath MD
Conflicts of interest: none

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