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All About BRASH!

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Abstract

BRASH (bradycardia, renal failure, atrio-ventricular nodal blocking agents, shock and hyperkalemia) Syndrome, a medical entity which has been described more recently, continues to be under-diagnosed. These manifestations do not occur in isolation but are inter-linked with synergistic effects on a susceptible patient. Being aware and having a high index of suspicion of the whole spectrum is important, just as managing all its components simultaneously for the desired outcomes. However, its variable presentation proves to be both a diagnostic and therapeutic clinical challenge. Hypovolemia and antihypertensive medications are the most common triggering factors for BRASH Syndrome. These factors may lead to pre-renal injury and hyperkalemia and when coupled with the AV blockers, can lead to the BRASH Syndrome cascade. In addition, the progression of renal failure can potentiate hyperkalemia and bradycardia from AV blockade. Electrocardiographical(ECG) changes can range from junctional bradycardia, heart blocks and classical changes of hyperkalemia.

BRASH Syndrome has been noted to have life threatening consequences if the vicious cannot be halted and the patient is not responsive to therapy. Understanding the pathophysiology, having a high index of suspicion and commencing simultaneous management for all its components is critical.

As BRASH Syndrome is relatively newly described and the literature continues to evolve around the topic we have decided to review the topic, collating findings from published case reports , to tap on the rich observations and findings reported by the authors. These, we find, can be extremely valuable, as we negotiate this exciting syndrome and learn more about it, from the scientific and clinical community.

Keywords: *BRASH, bradycardia, renal failure, shock, hyperkalemia, beta-blockers, calcium channel blockers*

Introduction

The recently coined BRASH syndrome was first reported by Josh Farkas in 2016. This syndrome is a pentad of bradycardia, renal impairment, atrioventricular (AV)-nodal blockers, shock and hyperkalemia. Over the years, more and more healthcare providers are increasingly able to recognize patients with BRASH syndrome and the number of cases reported over the years have increased.(1)

BRASH syndrome typically occurs when there is an insult to patients with underlying renal impairment taking AV-nodal blockers. The presence of both hyperkalemia secondary to renal impairment and AV-node blockade can dramatically produce bradycardia. This triggers a vicious cycle of renal hypoperfusion and dysfunction, hyperkalemia, conduction blockade and eventually, multiorgan dysfunction (1) (Fig 1).

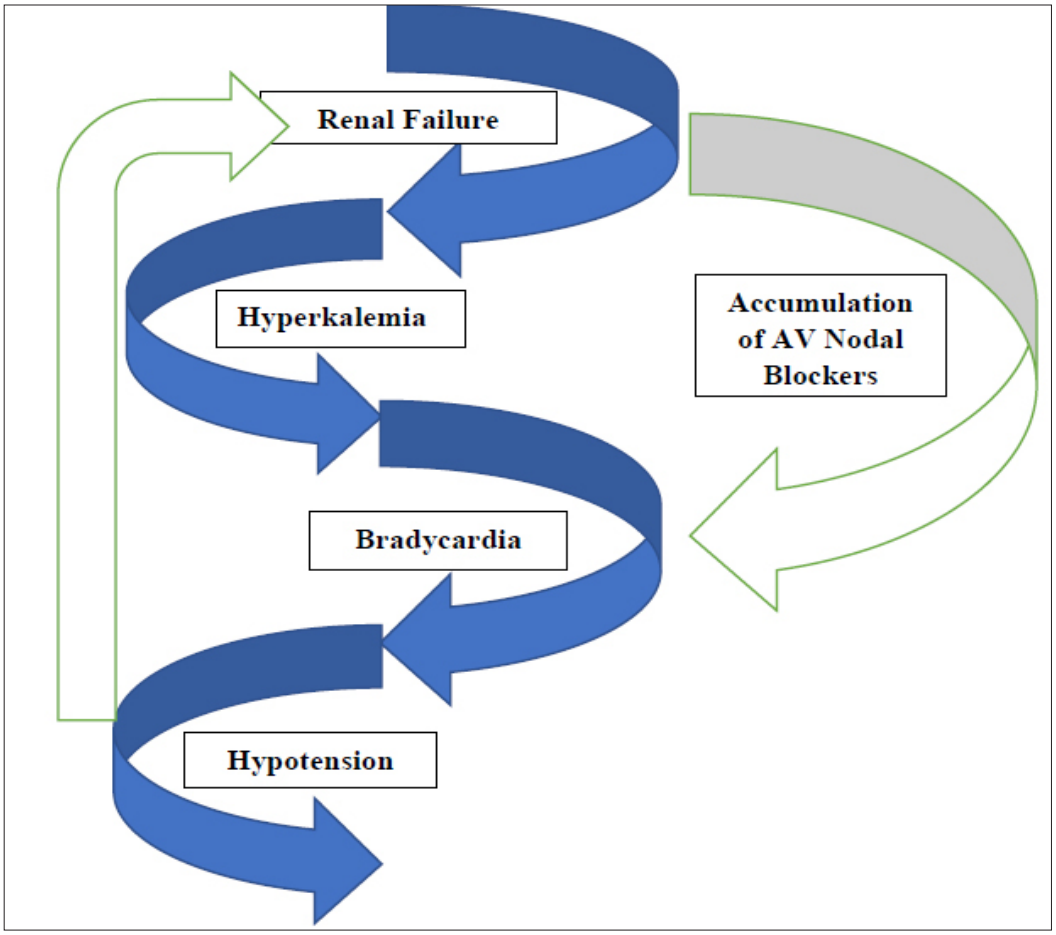

Fig1. BRASH Syndrome

Despite the paucity of knowledge on this syndrome, administration of the appropriate management usually results in good outcomes. However, there are cases whereby patients are refractory to standard therapy or patients recover with residual renal or cardiac dysfunction. Nonetheless, this article aims to consolidate and analyze various case reports of BRASH syndrome over the years and equip clinicians with the skills and knowledge to identify and manage this syndrome to improve clinical outcomes for the patients.

Methods

A search on PubMed for articles and case reports on BRASH syndrome up to March 2021 was performed. Search terms included "BRASH syndrome", "bradycardia", "atrioventricular block", "renal failure", "renal dysfunction", "hyperkalemia". Among the 492 articles, only 14 articles were related to BRASH syndrome. In addition, searching through the references of these 14 articles yielded another 15 articles. Among 29 articles, 1 was a letter, 2 were reviews, and the rest of the 26 case reports. In this review, 27 case reports (including the letter with the sharing of a case) were analyzed. As some submissions reported more than one case, the total number of cases analyzed was 33.

Results

Demographics

Among the 32 patients with BRASH syndrome, the average age is 68 years old with a range from 24 to 97 years old. Proportion of both genders is relatively similar, with 15 males and 16 females.

Medical Comorbidities and Medications

The full list of medical conditions are listed on [TABLE 1]. However, the significant conditions involved in the pathophysiology in BRASH syndrome are highlighted into two groups - (1) cardiac conditions, and (2) renal conditions. As such, the analysis done is based on these two clinical entities.

In all the reported cases of BRASH syndrome, 32/32 patients suffered from some form of cardiac condition, the most common being hypertension (27/32), followed by atrial fibrillation (9/32), and congestive cardiac failure (6/32). 8 of the 32 cases do suffer from other cardiac conditions including valvular problems or ischemic heart disease.

17 of the 32 cases have some form of renal impairment ranging from Chronic Kidney Disease (CKD) to End-Stage Renal Disease (ESRD) requiring renal replacement therapy.

In the 29 cases where medication list was provided, the most common cardiac medications taken was beta-blocker (19/29), followed by calcium channel blockers (CCBs) (15/29), and lastly, Angiotensin Converting Enzyme inhibitors/Angiotensin receptor blockers (ACEi/ARBs) (14/29). Among these 29 patients, 3 of them are on both ACEi/ARBs and CCB, 8 on both beta-blockers and CCB, 9 on ACEi/ARBs with beta-blockers, and 1 on a triple drug regimen. The rest of the patients are on a single drug therapy.

In addition, 6 of these patients have a recent change in drug regimen – beta-blocker (2), verapamil (3, 4), antibiotics (5), Non-Steroidal Anti-Inflammatory Drugs (NSAID) (6), metolazone (7))

Presentation and Initial Vital Signs

Across all 30 cases, majority (24/30) of the patients present with some form of neurological complains, including syncope, generalized weakness, giddiness, and loss of consciousness. 8 of these patients presents with cardiac symptoms [TABLE 2]. Other systemic manifestations leading to presentation ranges from GI-related symptoms to non-specific complains like fatigue and poor oral intake. 15 cases reported as such.

Initial vitals taken either in the field or in the healthcare setting demonstrated bradycardia in all patients (i.e. Heart rate <60), with 18 patients presenting with heart rate of 40 and below. Among the 25 patients, 20 were hypotension (i.e. Blood pressure <120/80). Interestingly, 3 and 4 of the cases were hypertensive and normotensive respectively.

Investigations

As BRASH syndrome typically results in renal impairment and electrolyte disturbances, particularly potassium, these 2 components are highlighted for analyses in this review article. 32 of the 33 reported cases had hyperkalemia and 1 had potassium levels at the high-end of the normal range (3.5-5.0mmol/L). Features suggestive of renal impairment was also noted as suggested by low eGFR (3/27), increased in BUN, creatinine, or urea levels (27/27).

In patients with hyperkalemia, progressive ECG changes would usually follow a characteristic pattern starting with peaked and tall T waves. However, such changes were seen in 7 cases. On the other hand, 13 of the patients present with varying degree of heart block (ranging from LBBB/RBBB to complete 3rd degree AV block). 11 patients had junctional bradycardia and 2 had sinus bradycardia. Surprisingly, 2 patients had unremarkable ECG reported.

Management

Pharmacological management of hyperkalemia includes the use of calcium gluconate/chloride to stabilize cardiac membranes in the presence of ECG changes, as well as the use IV insulin with IV dextrose to shift potassium intracellularly. Other adjuncts such as potassium binding resins and salbutamol are used. Among the 32 cases, 25 started on treatment for hyperkalemia [TABLE 3]. In view of the hemodynamic instability, 17 of them needed vasopressors. Additionally, 11 patients required the use of pacing (6/32 transcutaneous, 4/32 transvenous, 1/32 did no specify). A handful of them (9/32) required hemodialysis for managing the refractory hyperkalemia.

Outcomes

Majority of the patients recovered from this episode with both laboratory values and ECG changes reverted back to normal. However, 2 patients ended up needing dialysis, 1 developed a bundle branch block, 1 had asymptomatic hyperkalemia, 1 needed pacing, and 2 died as a result.

Table1. *Demographics and relevant medical conditions of the patients with BRASH syndrome*

S/N	Case report	Age	Gender	Cardiac conditions	Renal conditions	Other conditions	ACEi/ARBs	Beta-blockers	CCB	Other medications
1	Argulian, 2009 (8)	79	Male	HTN	-	Dementia Alcohol abuse GERD UBGIT	-	Metoprolol	Amlodipine	Donepezil
2	Arif, 2020 (9)	55	Female	HTN	CKD	DM	-	-	Diltiazem	Hydralazine Bumetanide Metolazone Atorvastation Insulin Glargine
3	Ata, 2021 (10)	64	Male	HTN Afib CAD HFrEF	CKD	DM	Sacubitril/ Valsartan	Bisoprolol	-	Furosemide Spironolactone
4	Aziz,2011 (11)	97	Female	HTN	-	DM Asthma	Valsartan	-	Amlodipine	Metformin Aspirin
5	Aziz, 2011	86	Female	HTN Afib	-	Asthma	-	-	-	-
6	Aziz, 2011	70	Male	HTN Afib	-	DM	Valsartan	Carvedilol	-	Spironolactone Insulin
7	Barreras, 2020 (12)	80	Female	AFib	-	DM	-	-	-	Apixaban
8	Bonvini, 2006 (13)	54	Female	HTN	-	DM	-	-	-	-
9	Diribe, 2019 (5)	51	Male	HTN HLD	RI	Pituitary CA Cushing's syndrome Hypothyroidism DM	-	-	-	TMP-SMX
10	Flores, 2020 (14)	74	Male	HTN	RI	DM	Lisinopril	Metoprolol	-	-
11	Golchin, 2018 (15)	84	Male	HTN	-	-	-	Beta-blocker	-	-
12	Grigorov, 2020 (16)	43	-	HTN Afib	-	NASH DM Bipolar	-	Metoprolol	Diltiazem	-
13	Hegazi, 2012 (3)	65	Female	HTN	DM nephropathy	DM	Valsartan	-	Verapamil	Aspirin Atorvastatin
14	Hegazi, 2012	57	Female	HTN	DM nephropathy	DM	Perindopril	-	-	-
15	Isabel, 2006 (17)	70	Male	HTN HF	Chronic RI	CLL DM	Enalapril	Metoprolol succinate	-	Spironolactone Furosemide Isosorbide mononitrate Simvastatin Metformin
16	Juvet, 2013 (18)	85	Female	-	-	-	Valsartan	Sotalol	-	Spironolactone TMP-SMX

17	Letavernier, 2006 (4)	63	Male	HTN LVH RBBB	Ciclosporin nephrotoxicity	Liver allograft	-	-	Verapamil	Calcium carbonate Trimetazidine Omeprazole Ferrous sulfate Rilmenidine EPO Ciclosporin Sodium polystyrene sulfonate
18	Letavernier, 2006	57	Male	ANVRT	Progressive renal failure	-	-	-	Verapamil	Calcium carbonate EPO
19	Letavernier, 2006	58	Male	HTN	ESRF	IBD	Ramipril	-	Verapamil Nicardipine	Azathioprine Pravastatin Calcium carbonate Citrate Zopiclone Darbeopoietin alpha
20	Liou, 2020 (19)	55	Male	HFrEF Persistent atrial flutter	CKD	Prior alcohol abuse	-	-	-	-
21	Miranid, 2008 (20)	77	Male	-	Questionable history of RI	DM Previous TURP	-	Propranolol	Diltiazem	Timolol and Xalatan eye drops
22	NH, 2017 (21)	81	-	HTN HLD IHD AFib	-	DM	-	Bisoprolol	Amlodipine	Amiodarone Rivaroxaban Ezetimibe Spironolactone Slow K Insulin
23	Prabhu, 2020 (22)	-	Female	HTN	CKD	-	-	Carvedilol	Verapamil	Aspirin
24	Sattar, 2020 (23)	66	Female	HTN HLD CAD	-	DM	-	Carvedilol	-	Aspirin Atorvastatin Clopidogrel Losartan Metformin-sitagliptin
25	Savage, 2020 (6)	81	Female	HTN	CKD	DM	Ramipril	Atenolol	-	-
26	Simmons, 2019 (2)	24	Male	HTN	Failed renal transplant on hemodialysis	-	-	-	-	-
27	Sohal, 2019 (24)	89	Female	HTN AFib HF	CKD	Stroke Hyperthyroidism	Lisinopril	Sotalol	Cardizem	-
28	Srivastava, 2020 (7)	62	Female	HTN HLD HF	CKD	Sleep apnea DM Depression	-	Carvedilol	Amlodipine	Bumetanide Isosorbide dinitrate Terazosin Hydralazine

29	Vishnu, 2021 (25)	60	Female	HTN	-	-	-	Atenolol	Amlodipine	-
30	Vuckovic, 2004 (26)	57	Male	Prior mitral valve replacement Cardiac bypass	-	Asthma	Fosinopril	Carvedilol	-	Digoxin Spironolactone Warfarin
31	Zaidi, 2019 (27)	88	Female	HTN CAD AFib HFpEF	-	Hypothyroidism Cerebrovascular accident	-	-	Amlodipine	Furosemide Isosorbide mononitrate Levothyroxine Metformin Omeprazole Ranolazine
32	Zimmers, 2002 (28)	78	Male	HTN Recurrent AFib	-	COPD Hypothyroidism	Lisinopril	Metoprolol	-	Potassium Levothyroixine Coumadin Simvastatin Albuterol
33	Zimmers, 2002	81	Female	Cardiomegaly with leaky heart valve HTN	-	DM Hypothyroidism	Enalapril	Atenolol	-	Furosemide Digoxin Glyburide Coumadin Amiodarone
		N = 32	N = 31	N = 32			N = 29			

ACEi/ARBs– Angiotensin converting enzyme inhibitors/Angiotensin II receptor blockers, AFib – Atrial fibrillation, AVNRT – AV nodal re-entrant tachyarrhythmia, CA – cancer, CAD – coronary artery disease, CCB – Calcium channel blockers, CKD – Chronic kidney disease, CLL – Chronic lymphocytic leukemia, COPD – Chronic obstructive pulmonary disease, DM – diabetes mellitus, EPO – Erythropoietin, ESRF – End-stage renal failure, GERD – Gastroesophageal reflux disease, HFpEF/HFrEF – heart failure with preserved/reduced ejection fraction, HLD – Hyperlipidemia, HTN – hypertension, IBD – Inflammatory bowel disease, IHD – Ischemic heart disease, LVH – Left ventricular hypertrophy, NASH – Non-alcoholic steatohepatitis, RBBB – right bundle branch block, RI – Renal insufficiency, TMP-SMX - Trimethoprim-sulfamethoxazole, TURP – Transurethral resection of the prostate, UBGIT – Upper bleeding gastrointestinal tract

Table2. *Presenting complains, vitals, and relevant laboratory investigations pertaining to BRASH syndrome*

S/N	Case report	Presentation (neurological)	Presentation (cardiological)	Presentation (others)	Initial vitals (HR/BP)	ECG changes	Hyperkalemia on ECG	Potassium levels	BUN, Cr, and eGFR
1	Argulian, 2009 (8)	Dizziness Syncope	-	Abdominal pain Diarrhea N/V	HR 28 BP 120/59	Complete AV block Escape rhythm ST segment depression with T wave inversion Prolonged QRS		6.4	BUN 58 mg/dL Cr 4.42 mg/dL eGFR 13ml/min
2	Arif, 2020 (9)	Increased drowsiness	Worsening SOB	Bilateral LL edema	BP 218/79	Unremarkable	-	5	BUN 116 mg/dL Cr 13.5 mg/dL
3	Ata, 2021 (10)	-	-	Fatigue Non-bloody diarrhea Vomiting Low oral intake	HR 28 BP 72/33	Bradycardia with junctional rhythm	-	5.8	Cr 625 mmol/L

4	Aziz, 2011 (11)	Dizziness Syncope	-	-	HR 56 BP 100/62	Sinus arrest Ventricular escape rhythm LAD	-	6.3	BUN 19 mg/dL Cr 1.6 mg/dL
5	Aziz, 2011	AMS	-	-	HR 30 BP 70/46	3rd degree heart block	-	5.7	BUN 67 mg/dL Cr 2.2 mg/dL
6	Aziz, 2011	Weakness	-	SOB	HR 38 BP 86/50	Sinus arrest High-grade heart block Junctional escape rhythm	-	6.1	BUN 47 mg/dL Cr 2.1 mg/dL
7	Barreras, 2020 (12)	Confused	-	-	HR 33 BP Low	-	-	5.3	Cr 1.9 mg/dL
8	Bonvini, 2006 (13)	Weakness	-	-	HR 22 BP 60/30	Junctional bradycardia No sinus activity Shortened QT interval	Peaked T waves	6.4	Cr 160 µmol/L
9	Diribe, 2019 (5)	Syncope	-	-	HR 20 BP 60/30	3rd degree AV block Widened QRS	Peaked T waves	8.6	BUN 51 mg/dL Cr 3.3 mg/dL
10	Flores, 2020 (14)	-	-	Chest rash Lip and hand swelling	HR 40 BP 60/30	Sinus bradycardia	-	7.1	CR 3.09mg/dL
11	Golchin, 2018 (15)	Weakness	-	Polyuria	-	-	-	7.1	AKI
12	Grigorov, 2020 (16)	Lethargy Unresponsive	PEA	Decreased oral intake	HR 35 BP 109/42	Complete heart block Sinus arrest Junctional bradycardia	-	7.6	Cr 2.75 mg/dL
13	Hegazi, 2012 (3)	Dizziness	-	Fever secondary to UTI	HR 48 BP 115/70	Junctional bradycardia	-	5.6	Urea 11 mM Cr 270 µm
14	Hegazi, 2012	Postural faintness	-	Fatigue	HR 44 BP 90/55	Junctional bradycardia	-	5.5	Cr 158 µm
15	Isabel, 2006 (17)	Fatigue	Exertional dyspnea New-onset bradycardia on ECG	Bilateral flank pain with tea-color urine	HR 48 BP 100/56	Junctional escape rhythm Widened QRS		6.5	Cr 3.3 mg/dL
16	Juvet, 2013 (18)	-	Hypotension Bradycardia	-	-	-	-	10.1	-
17	Letavernier, 2006 (4)	LOC	-	-	-	3rd degree AV block	-	6.8	-
18	Letavernier, 2006	-	-	-	-	LVH LBBB 3rd degree AV block	-	6.41	-
19	Letavernier, 2006	LOC	-	-	-	3rd degree AV block	-	6.7	-
20	Liou, 2020 (19)	-	-	-	-	-	-	6.8	Cr 1.6 mg/dL
21	Miranid, 2008 (20)	Near syncope Lightheadedness	-	-	HR 30 BP 92/34	Complete heart block Junctional escape rhythm	-	6.7	-

22	NH, 2017 (21)	Giddiness Lethargy	Chest discomfort	-	HR 33 BP 165/74	Absent P wave Slow ventricular rate	-	5.8	Urea 29.4 mmol/L Cr 272 mmol/L
23	Prabhu, 2020 (22)	-	-	-	HR 33 BP 80/45	Junctional rhythm	-	6.8	BUN 64 mmol/L Cr 3.1 mg/dL
24	Sattar, 2020 (23)	Lightheadedness Near syncope	-	-	HR 35 BP 87/62	Sinus bradycardia	-	6.2	BUN 34 mg/dL Cr 2.21 mg/dL
25	Savage, 2020 (6)	Dysarthric	Bradycardia	-	HR 29 BP 100/60	Ventricular escape rhythm RBBB	Mild peaking of T waves	8.3	eGFR 12ml/min (baseline 30)
26	Simmons, 2019 (2)	Syncope	-	Anuria for few days	Unremarkable	Unremarkable	-	7.4	-
27	Sohal, 2019 (24)	Weakness	Bradycardia	-	HR 35 BP 84/50	-	-	8.6	BUN 98 mg/dL Cr 6.11 mg/dL
28	Srivastava, 2020 (7)	Weakness	Bradycardia	-	HR 31 BP 63/32	Junctional rhythm	-	8	BUN 76 mg/dL Cr 4.06 mg/dL
29	Vishnu, 2021 (25)	Syncope	-	Abdominal pain Recurrent vomiting	HR 32 BP 100/70	Sinus bradycardia with junctional rhythm	-	6.19	BUN 188 mg/dL Cr 7.6 mg/dL
30	Vuckovic, 2004 (26)	Near syncope	-	SOB "Not feeling right"	HR 48 BP 100/60	Ectopic Atrial rhythm with AV dissociation	Larger than normal T waves	6.8	BUN 47 mg/dL Cr 2.7 mg/dL
31	Zaidi, 2019 (27)	-	-	Abdominal pain N/V	HR 40 BP 120/54	Junctional bradycardia Prolonged QTc	-	6.8	Cr 1.6 mg/dL eGFR 32ml/min
32	Zimmers, 2002 (28)	-	-	LOW	HR 40 BP 120/60	Junctional bradycardia Wide QRS	Tall widened T waves	7.4	BUN 105 mg/dL Cr 8.5 mg/dL
33	Zimmers, 2002	-	-	SOB	HR 52 BP 172/110	Junctional bradycardia	-	6	BUN 50 mg/dL Cr 2.1 mg/dL
		N = 30			N = 27	N = 28		N = 33	

AMS – Altered mental status, AV – Atrioventricular, BP – Blood pressure, HR – Heart rate, LAD – Left axis deviation, LBBB – Left bundle branch block, LL – Lower limb, LOC – Loss of consciousness, LOW – Loss of weight, LVH – Left ventricular hypertrophy, N/V – Nausea/vomiting, PEA – Pulseless electrical activity, RBBB – Right bundle branch block, SOB – Shortness of breath, UTI – Urinary tract infection

Table3. *Management and Outcomes*

S/N	Case report	Hyperkalemia management	Vasopressors	Pacing	Dialysis	Outcomes (√ if recovery to baseline)
1	Argulian, 2009 (8)	√	-	-	-	√
2	Arif, 2020 (9)	√	√	Transcutaneous	√	Discharged and declared ESRD needing dialysis
3	Ata, 2021 (10)	√	√	-	√	Cardiac arrested and did not survive
4	Aziz, 2011 (11)	√	-	-	-	√
5	Aziz, 2011	√	√	Transvenous	-	√
6	Aziz, 2011	√	-	-	-	√
7	Barreras, 2020 (12)	-	√	Transcutaneous	-	Developed 3 PEA, ROSC, but did not survive the 4th code
8	Bonvini, 2006 (13)	√	√	External pacemaker	-	√
9	Diribe, 2019 (5)	√	√	-	-	√
10	Flores, 2020 (14)	√	-	-	-	√
11	Golchin, 2018 (15)	√	√	-	√	√
12	Grigorov, 2020 (16)	√	√	Transcutaneous then transvenous	√	√
13	Hegazi, 2012 (3)	√	-	-	-	√
14	Hegazi, 2012	√	-	-	-	√

15	Isabel, 2006 (17)	√	-	Transcutaneous	√	√
16	Juvet, 2013 (18)	√	-	-	√	√
17	Letavernier, 2006 (4)	-	-	-	-	Recurrent asymptomatic hyperkalemia (K > 7mmol/L)
18	Letavernier, 2006	-	√	-	-	Develops supraventricular arrhythmia and pacing was indicated
19	Letavernier, 2006	-	-	-	√	√
20	Liou, 2020 (19)	√	-	-	-	-
21	Miranid, 2008 (20)	√	-	-	-	√
22	NH, 2017 (21)	-	√	-	-	-
23	Prabhu, 2020 (22)	√	√	-	-	√
24	Sattar, 2020 (23)	√	√	Transcutaneous	-	√
25	Savage, 2020 (6)	-	√	-	√	√
26	Simmons, 2019 (2)		√	Transvenous	-	√
27	Sohal, 2019 (24)	√	√	Transvenous	-	Labs and ECG normalized, however, now needing dialysis
28	Srivastava, 2020 (7)	√	√	-	-	√
29	Vishnu, 2021 (25)	√	√	-	√	√
30	Vuckovic, 2004 (26)	-	-	-	-	-
31	Zaidi, 2019 (27)	√	-	-	-	√
32	Zimmers, 2002 (28)	√	-	Temporary pacemaker	-	Recovered, with ECG showing new bundle branch block
33	Zimmers, 2002	-	-	-	-	√
		N = 32				N = 30

ESRD – End-stage renal disease, PEA – Pulseless electrical activity, ROSC – Return of spontaneous circulation

Discussion

Pathophysiology Behind BRASH Syndrome

The key pathophysiological process behind BRASH syndrome, as described by Farkas et al, stems from the bradycardia precipitated by the synergistic effects of hyperkalemia and AV-nodal blocking agents (1, 29). Presence of this bradycardia reduces cardiac output and renal perfusion, thereby causing renal impairment and worsens the hyperkalemia. This sets off a vicious cycle that can eventually lead to multiorgan involvement, leading to shock and death. This synergistic effect plays an important role because the cycle can be precipitated without markedly elevation in potassium levels or a significantly higher dose of AV-nodal blocking agents (5).

Triggers of BRASH Syndrome

BRASH syndrome often occurs when there is an acute renal insult in patients with a background of renal impairment. These triggers can include medications including ACEi/ARBs, beta-blockers, and calcium channel blockers as well as hypovolemia and infections (1, 7, 16, 29). Among the 33 reported cases, 6 of these patients were noted to have a recent change in medications – including increasing in the dose of antihypertensives (2-4), use of NSAIDs that could worsen renal function (6), and as part of the treatment for infections (5). Regardless of the triggers, these outcomes typically result in an overall hyperkalemic state, thereby enhancing the effects of AV-nodal blocking agents and setting off the vicious cycle in BRASH syndrome (1, 7).

Elderly patients are at a higher risk of developing BRASH syndrome given their multiple comorbidities and polypharmacy. Additionally, the presence of age-dependent decrease in renal function can further contribute to increased susceptibility to BRASH syndrome. Given that the average age of patients with this syndrome is 68 years old and majority are on multiple medications with a long list of medical comorbidities, it is important to know how these patients present to prevent poor clinical course and outcomes (9, 11).

Presentation of BRASH Syndrome

The most common presentation of patients with BRASH syndrome are the neurological complains including syncope, dizziness, and generalized weakness. With reference to the pathophysiology behind BRASH syndrome, the decreased cardiac output can lead to hypoperfusion in various end-organs, including the brain. In addition, hypoperfusion in various end-organs can result in non-specific complains as seen in this review of the 33 cases.

Bradycardia is a typical feature seen in severe hyperkalemia when potassium levels are beyond

7 mEq/L. In patients purely with hyperkalemia (≥ 5.5 mEq/L), the typical ECG changes starts with tall peaked T waves, followed by involvement of the atria as evidenced by P wave and PR segment changes. In severe hyperkalemic state, conduction abnormalities and bradycardia can be observed on ECG. However, BRASH syndrome patients do not follow the typical progression seen in hyperkalemia and presents with conduction blockade. In the 33 cases, 13 demonstrated some degree of AV-nodal block, with 11 junctional bradycardia and 2 with sinus bradycardia. The inability for the heart to function properly as a pump significantly reduces cardiac output, leading to hemodynamic inability and shock. In a very recent paper, Prabhu V et al described BRASH as an uncommon clinical presentation of COVID 19. (22)

Management of BRASH

Early identification and recognition of BRASH syndrome is important as patients may be refractory to standard management. This is particularly important as managing the various components of BRASH syndrome together early can halt the vicious cycle (1, 6).

The mainstay of managing BRASH syndrome is to manage the underlying triggers (eg. sepsis, hypovolemia, change in drug dosages), lower serum potassium levels and improve renal perfusion. Discontinuation of the triggering medications and underlying infection can interrupt the cascade. Use of drugs to shift potassium intracellularly and increase excretion plays an important role in reducing the synergistic effects with AV-nodal blocking agents. As hyperkalemia can lead to myocardial membrane instability, the use of calcium can provide membrane potential stability and prevent the progression of arrhythmias. More importantly, aggressive fluid resuscitation in volume-depleted patients can improve outcomes (5, 29). One common issue faced with the management of BRASH syndrome is the fixation on a single component only and managing only that. When the other factors are overlooked, patient might be under-resuscitated and thus not receive the complete management they should be getting. Therefore, looking at the bigger picture and a coordinated approach to management is important

Atropine is used as part of the Advanced Cardiovascular Life Support (ACLS) algorithm for bradycardia. This medication works by blocking the parasympathetic innervation via the vagus nerve. However, as there is little influence vagal tone has in BRASH syndrome, atropine may not be useful (16, 29, 30). Our review of these cases also showed that most patients are not responsive to atropine and subsequently. required vasopressors.

Some patients may present with normal blood pressure despite the significant bradycardia. These patients may be compensating for their bradycardia with a vasoconstrictive response, such that their blood pressure appears to be maintained. However, it is important to be aware that despite the normal blood pressure, they will continue to have mal-perfusion or hypo-perfusion. In view of this the treatment for the bradycardia (despite normal blood pressure) must include re-establishing the systemic perfusion and thus renal function. Fluid balance is a critical issue in these patients and hypovolemia is a common inciting cause as well. Whereas fluid replacement and maintaining perfusion is part of the management, it is important to be cognizant that some patients with BRASH syndrome can progress quickly to oliguric renal failure and subsequently retain fluid, leading to a volume overload state. Thus fluid status must be assessed as accurately as possible, through a good history, examination and may also include using tools such as the bedside ultrasound scan.

Interestingly, compared to the 20 patients who did not undergo pacing, the 11 patients who had pacing also recovered with adequate fluid resuscitation and treatment of hyperkalemia. This suggest that with aggressive management of the renal impairment, and hyperkalemia, patients are able to recover and pacing might not be necessary (16). This also means the patients should be monitored very closely in the early stages of management in order to make the necessary interventions at the appropriate time.

Outcomes of Management

Given that majority of the patients do recover from BRASH syndrome without significant impairment, long-term management of these patients should be aimed at discontinuing any triggering medications and to avoid acute kidney injury. However, minority of these patients went on to develop ESRF requiring renal replacement therapy or conduction abnormalities requiring lifelong follow up. 2 of the patients had cardiac arrest and were not able to survive despite resuscitation. This further highlights the importance of

identifying this syndrome early so that the appropriate treatment can be administered early and to reduce the mortality and morbidity.

The differential diagnoses for BRASH syndrome may initially include beta blockers overdose or isolated hyperkalemia from renal impairment. In differentiating beta blockers overdose, the levels of the drugs as well as the doses will be high. In contrast, for BRASH syndrome, the beta blockers doses are usually normal. In isolated hyperkalemia, there may ECG changes related to this, but with BRASH often the bradycardia may be very significant and out of proportion to the level of potassium.

Conclusion

Despite the recent increase in the number of reported cases, BRASH syndrome is still an under-recognized syndrome in which there are multiple variable presentation. A high index of suspicion is needed amongst clinicians in order to diagnose it. As the number of reported cases increases, more information can be obtained to do a large-scale study to establish diagnostic criteria and algorithms. With earlier identification of this syndrome, fast and appropriate management can be administered to patients, improving outcomes and reducing the need for delayed or unnecessary treatment.

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