CASE REPORT

Systolic heart failure in a patient with primary aldosteronism

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SUMMARY

A 53-year-old African man with a 25-year history of uncontrolled hypertension and systolic heart failure presented with an acute congestive heart failure exacerbation. He was found to have severe hypokalaemia, so additional testing was performed, and primary aldosteronism was confirmed. CT scan showed a 1.2×2.4 cm well-defined, homogeneous adenoma of the left adrenal gland. Adrenal vein sampling confirmed unilateral primary aldosteronism with lateralisation to the left adrenal gland. The patient was started on spironolactone and was referred to surgery for laparoscopic left adrenalectomy. Primary aldosteronism is associated with high cardiovascular morbidity and mortality due to activation of cardiac mineralocorticoid receptors. Studies suggest these negative effects can be reduced with early intervention and treatment. This case highlights the importance of investigating secondary causes of hypertension in young patients and the potential adverse cardiac effects of primary aldosteronism when it goes undiagnosed and untreated for years.

BACKGROUND

Primary aldosteronism (PA) is the most common cause of secondary hypertension with a prevalence that ranges from 5% to 11% in patients with hypertension (HTN).^{1–3} Even with this high prevalence, the diagnosis is often delayed or missed, which can lead to serious cardiovascular disease. Studies have shown that cardiovascular mortality is the leading cause of death in PA.^{1–4} Interestingly, the adverse cardiovascular effects of aldosteronism are at least partly independent of blood pressure and HTN. The main cardiac effects are mediated through the activation of mineralocorticoid cardiac receptors; long-standing stimulation of these receptors by aldosterone leads to myocardial fibrosis, ventricular remodelling and eventual congestive heart failure (CHF).⁵ We present a 53-year-old man with a 25-year history of uncontrolled HTN and CHF, who unfortunately was never evaluated for causes of secondary hypertension, despite presenting with the disease at a young age.

CASE PRESENTATION

A 53-year-old African man with a medical history of hypertension diagnosed in his mid-20s, systolic CHF and non-ischaemic cardiomyopathy presented with worsening exertional dyspnoea, lower extremity oedema, paroxysmal nocturnal dyspnoea and

orthopnoea for approximately 1 week. The patient was on six hypertensive agents as an outpatient including clonidine, hydralazine, isosorbide mononitrate, valsartan and furosemide. Despite compliance with medications, he had frequent admissions for CHF exacerbations. He denied tobacco, drug or alcohol use. Although he was diagnosed with hypertension at a young age, the patient did not recall having additional testing for secondary causes of HTN at the time of diagnosis. He did recall a diagnosis of chronic hypokalaemia, which had been attributed to furosemide use, and he had been prescribed potassium supplements intermittently in the past. He denied any known family history of PA or uncontrolled HTN. Vital signs revealed a blood pressure of 163/103 mm Hg, heart rate of 74 beats per minute, respiration rate of 17 and 95% oxygen saturation on 3 L nasal cannula. Pertinent findings on physical examination included jugular venous distention, bilateral lower extremity pitting oedema, bilateral rales and a prominent S3 gallop.

INVESTIGATIONS

EKG showed no acute ischaemic changes, sinus rhythm with chronic left bundle branch block. Troponins were negative on three consecutive occasions. Chest X-ray revealed bilateral pulmonary vascular congestion. Transthoracic echocardiography revealed moderate left ventricular hypertrophy and dilatation with global hypokinesis and an ejection fraction of 10%–15%. No valvular abnormalities were noted. Cardiac MRI showed areas of myocardial fibrosis likely related to hypertrophy, atypical for ischaemic disease and atypical for previous infarct or amyloidosis (figure 1). Laboratory studies showed serum potassium of 2.6 mmol/L and bicarbonate of 34 mmol/L. PA was suspected, and further testing revealed an elevated plasma aldosterone level of 154 ng/dL (normal less than 39.2 ng/dL), a decreased plasma renin activity (RA) of less than 2.1 ng/mL/hour and a plasma aldosterone concentration/plasma RA (PAC/PRA) ratio of 73.3 (ng/dL)/(ng/mL/hour).

Results of an overnight dexamethasone suppression test, thyroid function testing and plasma and urine metanephrines were normal. An oral salt loading suppression test was not performed for fear that it would exacerbate his pulmonary oedema and heart failure. CT of the abdomen and pelvis with contrast showed a 1.2×2.4 cm well-defined, homogeneous adenoma of the left adrenal gland (figures 2 and 3). Subsequent adrenal vein sampling confirmed unilateral PA with lateralisation to the left adrenal gland

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Figure 1 Sagittal view of cardiac MRI revealing marked concentric left ventricular hypertrophy with areas of delayed myocardial enhancement representing fibrosis related to hypertrophy and in a distribution atypical for ischaemic disease/prior infarct and atypical for amyloidosis.

(table 1.) The adrenal vein cortisol to inferior vena cava cortisol ratio for both the left and right adrenal vein was greater than 3, consistent with successful adrenal vein cannulation. The left and right adrenal vein aldosterone to adrenal vein cortisol ratio were 14.8 and 2.2, respectively. A lateralisation ratio greater than 4 is consistent with unilateral disease, whereas a lateralisation ratio less than 3 is consistent with bilateral disease. Our patient's lateralisation ratio of left to right was 6.7, consistent with unilateral disease (table 1). The patient was started on spironolactone treatment with improvement of his blood pressure, and hypokalaemia and was referred for left adrenalectomy.

DISCUSSION

PA is the most common and curable form of secondary hypertension, but the diagnosis may be missed or delayed. Long-standing and prolonged activation of cardiac mineralocorticoid receptors (MRs) by aldosterone can lead to cardiovascular disease,

Figure 2 Coronal view of CT abdomen/pelvis with contrast showing a 1.2x2.4 cm well-defined, homogeneous adenoma of the left adrenal gland with rapid enhancement and washout of contrast.

Figure 3 Axial view of CT abdomen/pelvis with contrast showing a 1.2x2.4 cm well-defined, homogeneous adenoma of the left adrenal gland with rapid enhancement and washout of contrast.

independent of blood pressure. MRs are expressed in multiple cell types in the heart, including cardiomyocytes, coronary endothelial and vascular smooth muscle cells, fibroblasts and inflammatory cells, such as macrophages.⁶ The function of the MR in the healthy heart is not fully understood but may include regulation of cardiomyocyte growth and cardiac electrophysiology.⁶

Prolonged exposure to elevated aldosterone has been shown to be associated with collagen deposition, myocardial fibrosis and ventricular remodelling.^{5,7,8} Activation of MR cardiac receptors may also play a role in myocardial hypertrophy and cardiac remodelling in patients with PA via mechanisms that include accelerated fibrosis and eventual heart failure.⁵ It is still unclear whether this myocardial fibrosis is reversible. However, in one small prospective study of 20 patients with PA, it was shown that those who underwent adrenalectomy had decreased collagen content in the myocardium.⁹

Evidence for the role of MR in the pathophysiology of cardiac disease and heart failure has come from cell-specific overexpression and deletion studies.⁶ In experimental animal studies, deletion or inactivation of the MR gene attenuated left ventricular dilatation, cardiac hypertrophy and development of systolic heart failure.⁶ Alternatively, overexpression of the MR in cardiomyocytes induced ventricular remodelling and the development of systolic heart failure.^{6,10}

The cardiovascular effects of MR activation by aldosterone are quite profound and are not limited to heart failure.

One study found a greater prevalence of cardiovascular events in 459 patients with PA versus patients with essential HTN,

Table 1 Results of adrenal vein sampling without cosyntropin stimulation, with sampling of each adrenal vein (AV) done with the inferior vena cava (IVC) simultaneously

Vein	Aldosterone (A), ng/dL	Cortisol (C), µg/dL	AV cortisol: IVC cortisol	A:C ratio	Adrenal lateralisation index
RT Adrenal vein	750	340	28.3	2.2	
LT Adrenal Vein	16500	1110	92.5	14.8	6.7
IVC	35	12		2.9	

LT, left; RT, right.

including heart failure (4.1% vs 1.2%; OR 3.5) myocardial infarction (4.4% vs 1.7%; OR 2.8), atrial fibrillation (3.9% vs 1.1%; OR 4.3) and coronary artery disease (5.7% vs 2.8%; OR 2.2).¹¹ Similarly, another study found a greater prevalence of cardiovascular events in 124 patients with PA versus patients with essential HTN including stroke (12.9% vs 3.4%; OR 4.2), myocardial infarction (4% vs 0.6%; OR 6.5) and atrial fibrillation (7.3% vs 0.6%; OR 12.1).¹²

Studies suggest that patients with PA suffer from more cardiovascular disease and the incidence of cardiovascular disease may decrease once aldosterone normalises. One study of 54 patients also found a higher prevalence of cardiovascular events in patients with PA versus patients with essential HTN with ORs of 4.93, 4.36 and 2.80 for sustained arrhythmias, cerebrovascular events and coronary artery disease, respectively.¹³ These patients were followed for 7 years, and the patients with PA were treated by either adrenalectomy or aldosterone antagonist therapy. Once the effects of excess aldosterone were reduced, the incidence of cardiovascular events for both groups became the same.¹³

The most recent guidelines suggest that screening for PA is recommended but not limited to patients with hypertension and hypokalaemia, severe hypertension (systolic above 150 mm Hg or diastolic above 100 mm Hg), uncontrolled hypertension despite three medications including a diuretic, hypertension with an adrenal adenoma and hypertension with a personal history or family history of premature hypertension. Once PA is confirmed, CT is recommended as in the initial study to exclude large masses that may represent adrenocortical carcinoma and to assist the interventional radiologist and surgeon with anatomic localisation as needed.¹ If an adrenal adenoma or adrenal thickening is present, screening for Cushing's or subclinical Cushing's syndrome may also be warranted. Our patient had no physical or biochemical findings suspicious for Cushing's, so no further work up for excess cortisol production was pursued.

One also needs to be mindful when interpreting RA and PAC/PRA ratio in patients who are already on medications that can affect these results, leading to false negatives and false positives. Renin levels are increased with diuretics such as furosemide, dihydropyridine calcium channel blockers, ACE inhibitors and angiotensin receptor antagonists, which can lead to false-negative results when evaluating for PA. However, RA can be decreased by beta blockers and clonidine, which can lead to false-positive results. It is unlikely that our patients' use of multiple hypertensive medications led to errors in his PAC/PRA ratio, which was markedly elevated.

The treatment for proven unilateral PA is unilateral laparoscopic adrenalectomy. Treatment for bilateral adrenal disease or for those unwilling to undergo surgery is with MR antagonist therapy, namely spironolactone or eplerenone.¹² MR blockade by spironolactone or eplerenone favourably affects cardiovascular outcomes.¹⁴ Clinical trials have revealed that those with elevated aldosterone levels and heart failure who are treated with aldosterone antagonist have decreased mortality.^{5 15 16} Although spironolactone is preferred, gynaecomastia may occur. Eplerenone is not associated with gynaecomastia, but it has only 50% of the MR antagonist potency of spironolactone and is more expensive than spironolactone.¹

Unfortunately, our patient was never screened for PA at the time of his diagnosis of hypertension, even though he met the criteria to be screened. We cannot conclude that our patient's frequent CHF exacerbations were a direct result of PA, nor can we conclude that his systolic CHF would have been prevented by earlier diagnosis and management of PA. However, it is possible that earlier treatment may have attenuated some of his cardiovascular disease.

Whether his cardiac fibrosis and heart failure will improve significantly or not after adrenalectomy remains to be seen.

Learning points

- ▶ Primary aldosteronism is a common cause for secondary hypertension (HTN) but still is sometimes missed.
- ▶ Patients with primary aldosteronism have a greater prevalence of cardiovascular disease than patients with essential HTN due to activation of cardiac mineralocorticoid receptors.
- ▶ Early recognition of the signs and symptoms of primary aldosteronism is essential not just to determine the cause for HTN but also to prevent cardiovascular morbidity and mortality.

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REFERENCES

- 1 Funder JW, Carey RM, Mantero F, *et al.* The Management of primary aldosteronism: case detection, diagnosis, and treatment: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2016;101:1889–916.
- 2 Rossi GP, Bernini G, Caliumi C, *et al.* A prospective study of the prevalence of primary aldosteronism in 1,125 hypertensive patients. *J Am Coll Cardiol* 2006;48:2293–300.
- 3 DeCarlo KE, Agrawal N. Double hit! A unique case of resistant hypertension. *BMJ Case Rep* 2017;2017:bcr-2017-221530.
- 4 Reincke M, Fischer E, Gerum S, *et al.* Observational study mortality in treated primary aldosteronism: the German Conn's registry. *Hypertension* 2012;60:618–24.
- 5 Catena C, Colussi G, Lapenna R, *et al.* Long-term cardiac effects of adrenalectomy or mineralocorticoid antagonists in patients with primary aldosteronism. *Hypertension* 2007;50:911–8.
- 6 Bauersachs J, Jaissner F, Toto R. Mineralocorticoid receptor activation and mineralocorticoid receptor antagonist treatment in cardiac and renal diseases. *Hypertension* 2015;65:257–63.
- 7 Funder JW. Aldosterone and mineralocorticoid receptors in the cardiovascular system. *Prog Cardiovasc Dis* 2010;52:393–400.
- 8 Rossi GP, Di Bello V, Ganzaroli C, *et al.* Excess aldosterone is associated with alterations of myocardial texture in primary aldosteronism. *Hypertension* 2002;40:23–7.
- 9 Lin YH, Wu XM, Lee HH, *et al.* Adrenalectomy reverses myocardial fibrosis in patients with primary aldosteronism. *J Hypertens* 2012;30:1606–13.
- 10 Lother A, Berger S, Gilsbach R, *et al.* Ablation of mineralocorticoid receptors in myocytes but not in fibroblasts preserves cardiac function. *Hypertension* 2011;57:746–54.
- 11 Savard S, Amar L, Plouin PF, *et al.* Cardiovascular complications associated with primary aldosteronism: a controlled cross-sectional study. *Hypertension* 2013;62:331–6.
- 12 Milliez P, Girerd X, Plouin PF, *et al.* Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. *J Am Coll Cardiol* 2005;45:1243–8.
- 13 Catena C, Colussi G, Nadalini E, *et al.* Cardiovascular outcomes in patients with primary aldosteronism after treatment. *Arch Intern Med* 2008;168:80–5.
- 14 Rossi G, Boscaro M, Ronconi V, *et al.* Aldosterone as a cardiovascular risk factor. *Trends Endocrinol Metab* 2005;16:104–7.
- 15 Pitt B, Zannad F, Remme WJ, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999;341:709–17.
- 16 Pitt B, Remme W, Zannad F, *et al.* Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;348:1309–21.

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