Primary hyperaldosteronism in a patient with end-stage renal disease

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Introduction

The prevalence of hypertension in patients on chronic haemodialysis has been reported to be as high as 90% [1]. Several aetiological factors may contribute to hypertension in this population including sodium and water retention, increased activity of vasoconstrictive systems and increased arterial stiffness [2]. Recent studies show that primary aldosteronism is common in patients with hypertension, being present in up to 10% of all hypertensive individuals [3]. Our understanding of the physiological and pathophysiological actions of aldosterone has changed in recent years, and increasing evidence identifies that its role in the pathogenesis of hypertension is beyond its effects on renal tubular cell-mediated ion transport and NaCl retention. Here, we present a case of hypertension secondary to primary aldosteronism in an anuric patient on chronic haemodialysis who showed a dramatic response to aldosterone receptor blockade.

Case

A 57-year-old African American male with a history of progressive chronic kidney disease secondary to poorly controlled hypertension and type 2 diabetes mellitus reached end-stage renal disease (ESRD) in May 2002, and was started on chronic haemodialysis. Despite concurrent treatment with a low salt diet, a medication regimen of clonidine 0.1 mg BID, terazosin 10 mg QD, felodipine 5 mg QD and fosinopril 80 mg QD, and aggressive ultrafiltration during haemodialysis treatments, his hypertension was poorly controlled [pre-dialysis blood pressure (BP) ranging from 152/93 to 161/98 mmHg]. Measurement of plasma aldosterone and renin revealed a high aldosterone level (12 ng/dl, normal: 2–9) with a suppressed direct renin level (<2 μU/ml, normal: 5–13 μU/ml), compatible with the diagnosis of primary hyperaldosteronism. Assessment of 24-h urinary aldosterone excretion could not be performed because the patient was anuric. Provocative testing with high dietary salt intake and/or synthetic mineralocorticoid administration was felt to be clinically contraindicated because of his severe hypertension and anuric ESRD.

The patient was started on spironolactone, 50 mg/day, in July 2002. Within 2 weeks, clinically evident changes in his pre-dialysis BP were observed. After 4 weeks, clonidine was discontinued and the fosinopril dose was reduced to 40 mg/day because of improved BP control, and shortly thereafter his felodipine was discontinued. Patient’s pre-dialysis BP stabilized around 120/60 mm Hg, and after 1 year, the spironolactone dose could be reduced to 25 mg/day and later to 12.5 mg/day, and the fosinopril dose was decreased to 10 mg PO QD. Plasma aldosterone and renin were measured 2 years after initiation of treatment and revealed normalization of levels (9 ng/dl and 4 μU/ml, respectively). The patient’s potassium level varying from 4.5 to 5.5 mmol/l (normal: 3.5–5.1 mmol/l) before starting spironolactone; he had no clinically significant episodes of hyperkalaemia.

Discussion

The majority of patients on chronic haemodialysis exhibit various stages of hypertension. While several aetiological factors can be distinguished in this population, one critical factor is intravascular volume expansion due to the lack of renal-mediated salt and water excretion [2]. However, in many patients adequate extracellular volume control is not sufficient to control hypertension. Other aetiological factors should then be sought for in order to establish an appropriate management strategy for control of hypertension in these patients.
Multiple factors contribute to the hypertension in patients with ESRD. For example, sympathetic system hyperactivity leads to hypertension by increasing peripheral vascular resistance [4]. Unfortunately, inhibition of the sympathetic nervous system, with β-adrenergic receptor antagonists with or without concomitant α-adrenergic receptor antagonists rarely results in substantial improvements in hypertension control in patients with ESRD. A second mechanism includes accumulation of asymmetric dimethyl arginine (ADMA), which contributes to hypertension by inhibiting synthesis of the potent vasodilator, nitric oxide [5]. At present, specific approaches in preventing ADMA accumulation in ESRD patients are not available.

The diagnosis of primary hyperaldosteronism relies on a combination of hypertension, spontaneous or diuretic-induced hypokalaemia, high concentrations of aldosterone in plasma or urine and low concentrations of renin [6]. The hallmark of diagnosis is the dissociation between aldosterone and renin concentrations as evidenced by an increase in plasma aldosterone–renin ratio [6,7]. The patient described in this report had difficult-to-treat hypertension despite use of multiple anti-hypertensive drugs and aggressive ultrafiltration, prompting us to seek for other aetiologies. He showed all the aforementioned criteria, except for hypokalaemia which is explained by his ESRD. Concerning the aldosterone–renin ratio, the cut-off value for a positive test depends on the measurement units used [8]. If aldosterone is measured as nanogram/decilitre and renin as microunits/millilitre, the cut-off value for a positive test would be 3.3 [8]. Our patient showed a high plasma aldosterone concentration with simultaneous suppressed renin, resulting in a plasma aldosterone–renin ratio of >6, confirming the diagnosis. Although some authors suggest performing confirmatory tests, there is no consensus as to whether suppression tests should be included in the definition of primary hyperaldosteronism [6]. As mentioned earlier, we chose not to perform these tests in our patient because of anuria and severe hypertension. Interestingly, once the diagnosis of primary hyperaldosteronism was made in this anuric patient, even low doses of spironolactone (12.5–50 mg/day) were followed by a dramatic decrease in pre-dialysis systolic and diastolic BP, necessitating discontinuation of the majority of his anti-hypertensive medicines.

It is important to emphasize that the effect of aldosterone was not mediated by inhibiting renal distal tubule sodium reabsorption and, consequently, through changes in plasma volume. We could exclude this possibility since the patient was anuric and renal sodium transport did not mediate a role in BP management in this patient. Although it is theoretically possible that spironolactone can alter colonic sodium transport [9], there were no significant changes in his apparent volume status or dry weight that would support such a proposed mechanism. Instead, this patient appeared to have improvements in his BP mediated through the extrarenal effects of spironolactone.

During the last decade, a new understanding for the breadth of actions of aldosterone has emerged. It is now well-known that aldosterone has physiological and pathophysiological effects in non-epithelial tissues, including the heart, vasculature and brain, that are independent of its effects on renal tubular cell ion transport [10]. Through mechanisms different from its effects on epithelial cell transport of sodium and potassium, aldosterone may mediate hypertension and cardiac fibrosis [11,12]. Increased plasma aldosterone concentrations are associated with decreased arterial compliance in hypertensive individuals [13], and patients with primary hyperaldosteronism exhibit a greater degree of endothelial dysfunction than do patients with essential hypertension [14]. The current case report thereby both confirms these experimental observations and demonstrates clinically the importance of aldosterone and BP maintenance in a patient in whom the effects on renal ion transport could be eliminated.

A second interesting observation in this case was that direct renin levels were suppressed prior to therapy, and then increased over time with effective treatment of the primary hyperaldosteronism. Suppressed renin release at the time of diagnosis enabled use of the plasma aldosterone–renin ratio for diagnosis of primary hyperaldosteronism. A normalization of the plasma renin level with treatment confirmed that the suppressed renin was not due to the patient having ESRD and lack renal renin production capacity. Indeed, an increasing number of studies demonstrate the importance of extrarenal renin production [15]. The ability to use the plasma aldosterone–renin ratio for diagnosis of primary hyperaldosteronism was critical in this patient. Confirmatory studies that are routinely recommended, such as 24 h urinary aldosterone excretion measurement, assessment of changes in plasma aldosterone and plasma renin in response to a high salt diet, and uses synthetic mineralocorticoids, could not be performed in this anuric ESRD patient with refractory hypertension. Many authors have suggested that the plasma aldosterone to plasma renin activity ratio can be effectively utilized for identifying patients with primary hyperaldosteronism [16]. The current observation adds to this body of literature, and extends it by demonstrating the utility of this measurement in an anuric patient with ESRD.

The incidence of primary hyperaldosteronism in ESRD patients is unknown. However, hypertension, particularly refractory hypertension, is common in patients with ESRD and the likelihood of primary hyperaldosteronism, at least in patients with adult chronic kidney disease, appears to parallel the severity of their hypertension [17]. The observation that almost 15% of patients with stage III hypertension have primary hyperaldosteronism [17] raises the important question as to whether primary hyperaldosteronism is present in a similar percentage of patients with ESRD.
If so, this could result in an important new avenue for treatment of the refractory hypertension that is so common in this patient population. However, mineralocorticoid receptor antagonists cannot be routinely recommended for patients with ESRD. Gross et al. [18] used moderate doses (100 mg/day) of spironolactone in eight hemodialysis patients for 2 weeks, and observed only a modest decrease in pre-dialysis systolic BP, from 142 mmHg to 131 mmHg, and no significant changes in pre-dialysis diastolic BP or post-dialysis BP measurements. However, these patients did not have primary hyperaldosteronism, and therefore, would not have been expected to have a substantial component of aldosterone-mediated hypertension.

It is also important to note that substantial evidence demonstrates that aldosterone can play a facilitating factor in the progression of chronic kidney disease, and that blocking mineralocorticoid receptors may have protective benefits in patients with chronic kidney disease [19,20]. Whether primary hyperaldosteronism contributed to this individual’s chronic kidney disease and ESRD, however, is only speculative at present.

Based on these observations, we suggest that a diagnosis of primary hyperaldosteronism be considered in a patient with ESRD in whom BP is not well-controlled with traditional management strategies. Screening can be performed with a plasma aldosterone–plasma renin ratio obtained at the time of initiation of a hemodialysis treatment session. If an elevated ratio is obtained, treatment with a mineralocorticoid receptor antagonist, such as spironolactone or eplerenone, might then be considered, even in patients who are anuric. Close observation follow-up of the patient’s serum potassium level is important during course of treatment.

Conflict of interest statement. None declared.

References

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