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Teaching Point
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Resistant hyponatremia and hypokalemia treated successfully with nephrectomy

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Introduction

Persistent hyponatremia and hypokalemia in the setting of hypertension may be a manifestation of an underlying hyperreninemic state. We present here a case of a patient who presented with a constellation of hypertension with severe polydipsia, subnephrotic proteinuria, with resistant hyponatremia and hypokalemia. Workup revealed an elevated plasma renin activity and elevated plasma aldosterone. Magnetic resonance imaging of the renal vasculature revealed complete occlusion of the right renal artery and a nuclear medicine renal scan showed a split renal function of 87% for the left kidney and 13% for the right kidney. The use of angiotensin receptor blockers (ARB) and angiotensin-converting enzyme (ACE) inhibitors was contraindicated due to a history of angioedema. Nephrectomy of the ischemic kidney was thus planned, and it resulted in a dramatic and complete resolution of his laboratory abnormalities and hypertension.

Case report

Our patient was a 51-year-old African-American male with a past medical history of hypertension and angioedema due to lisinopril, was referred to the nephrology service for generalized weakness, severe headache, shortness of breath with associated polyuria (4 L) and polydipsia. Prior to his present admission, the patient has had multiple in-hospital admissions for similar complaints over the past 4 months.

On examination, his blood pressure was 200/100 mmHg with orthostatic hypotension. There was no papilloedema, renal bruit or peripheral edema. Initial investigations (International Unit; Reference ranges) revealed serum sodium of 122 mEq/L (122 mmol/L; Reference range: 137–145 mEq/L), potassium of 3.7 mEq/L (3.7 mmol/L; Reference range: 3.5–5.1 mEq/L), bicarbonate of 29 mEq/L (29 mmol/L; Reference range 22–30 mEq/L), serum osmolality of 253 mosm/kg (253 mmol/kg; Reference range: 280–296 mosm/kg), a corresponding urine osmolality of 111 mosm/kg (111 mmol/kg; Reference range: 50–1200 mosm/kg) and a spot urine protein/creatinine ratio of 1.8 g (Table 1). Ultrasound of the kidneys revealed an asymmetrically shrunken right kidney of size 7.7 $\times$ 4.4 $\times$ 3.5 cm, with a normal left kidney of size 11.6 $\times$ 6.2 $\times$ 6.3 cm.

Initially, the patient's hyponatremia was attributed to polydipsia secondary to dry mouth (from clonidine), and hypokalemia was attributed to the use of hydrochlorothiazide. In addition, orthostatic hypotension was related to clonidine [1]. Even though both the medications were discontinued about a month prior to his present admission, electrolyte abnormalities with signs and symptoms persisted. Fluid restriction to $<$500 mL/day and potassium supplementation failed to resolve his electrolyte abnormalities (Table 2) and a combination of Amlodipine, Metoprolol, Hydralazine and Spironolactone failed to control hypertension.

Additional workup revealed an elevated plasma renin activity of 5551 ng/mL/h (1542 ng/L/s; Reference range: 20–160 ng/mL/h) with a corresponding elevated plasma aldosterone of 54.3 ng/dL (1.5 nmol/L; Reference range: $\leq$16 ng/dL). The magnetic resonance imaging of the renal vasculature revealed complete occlusion of the right renal artery. Nuclear medicine renal scan showed a split renal function of 87% for the left kidney and 13% for the right kidney.

Constellation of renovascular hypertension with severe polydipsia, hyponatremia and hypokalemia led to the probable diagnosis of hyponatremic hypertensive syndrome (HHS). In view of history of angioedema secondary to lisinopril, angiotensin II receptor blockers or direct rennin inhibitor were avoided. The patient underwent a unilateral laparoscopic right nephrectomy (the ischemic nonfunctioning kidney) and post-operative showed his renin activity decreased to $<$20 ng/dL/h with a corresponding aldosterone of 1.9 ng/dL. Within 1 month of post-surgery, his blood pressure was controlled on amlodipine 5 mg, along with complete normalization of all electrolyte abnormalities and associated signs and symptoms.

Discussion

As early as in 1965, Brown *et al.* [2] had described HHS—a combination of severe resistant hypertension along with hyponatremia, hypokalemia, polyuria and proteinuria—sometimes in the nephrotic range [2, 3]. Subsequent case

Table 1. Summary of the pertinent laboratory results[a]

Sodium	122 mEq/L (122 mmol/L; 137–145 mEq/L)
Potassium	3.7 mEq/L (3.7 mmol/L; 3.5–5.1 mEq/L)
Bicarbonate	29 mEq/L (29 mmol/L; 22–30 mEq/L)
Blood urea nitrogen	10 mg/dL (3.57 mmol/L; 9–20 mg/dL)
Creatinine	1.0 mg/dL (88.4 μmol/L; 0.6–1.2 mg/dL)
Calcium	9.1 mg/dL (2.27 mmol/L; 8.4–10.3 mg/dL)
Magnesium	1.7 mg/dL (0.85 mmol/L; 1.6–2.3 mg/dL)
Phosphorus	3.1 mg/dL (1 mmol/L; 2.5–4.5 mg/dL)
Serum osmolality	253 mosm/kg (253 mmol/kg; 280–296 mosm/kg)
Urine osmolality	111 mosm/kg (111 mmol/kg; 50–1200 mosm/kg)
Spot urine protein creatinine ratio	1.8
Urine sodium	24 mEq/L (24 mmol/L; 30–90 mEq/L)
Urine chloride	29 mEq/L (29 mmol/L)

[a]US conventional unit with (International Unit; Reference ranges) in brackets.

Table 2. Summary of blood pressure and prominent electrolyte abnormalities during the hospital stay[a]

	Day 1	Day 2	Day 5	Day 25: day of surgery	Day 30
SBP	190	205	160	190	137
DBP	80	100	96	100	78
Sodium	122	122	125	134	136
Potassium	3.7	2.8	2.4	2.8	4.5

[a]Unilateral nephrectomy of the ischemic kidney resulted in complete and dramatic resolution of the signs, symptoms and laboratory abnormalities. Sodium and potassium values in mmol/L. SBP, systolic blood pressure; DBP, diastolic blood pressure in mmHg.

reports and studies documenting this constellation of symptoms have not been common, especially in the adult population. More recently, a similar syndromic entity has also been described to occur in pre-eclampsia by Sandhu *et al*. [4]. In addition, there have been case reports of HHS as a paraneoplastic manifestation of tumors such as renin-producing leiomyosarcomas [5]. Overall, HHS still remains an under diagnosed entity.

The classical presentation of HHS includes hyponatremia (serum sodium $<$ 136 mmol/L) in the setting of hypertension (systolic blood pressure $>$ 165 mmHg and diastolic $>$ 95 mmHg with or without anti-hypertensive medication) with evidence of renal ischemia [6]. History of heavy smoking is considered as a significant risk factor [7]. An elevated rennin level, likely secondary due to renal ischemia, is also a pathognomonic laboratory finding. As was the case in our patient, if the renal ischemia is unilateral, the elevation in systemic arterial pressure can induce pressure natriuresis via the normal kidney leading to hyponatremia and volume depletion. The latter will in turn lead to a further increase in renin production. Similarly, increased rennin will increase production of angiotensin II and thus aldosterone which via its action on the collecting tubules of the normal functioning kidney can lead to persistent hypokalemia. Hypokalemia itself can in-turn act as a stimulant for enhanced rennin production.

A persistently elevated level of angiotensin II cannot only act directly on the renal tubules to cause water absorption but can directly stimulate the thirst center in the brain leading to increased production of antidiuretic hormone (ADH). The combination thus explains the resistant dilutional hyponatremia. Smoking is a significant risk factor for HHS not only by contributing to atherosclerotic renovascular disease but also by the fact that nicotine is a potent stimulus for ADH [8]. Increased angiotensin II may play a significant role in proteinuria in HHS patients.

Therapeutic options in a patient with HHS include pharmacological options and surgical options. Using ACE inhibitors, ARBs or direct rennin inhibitors is reasonable when you take into account that high rennin levels are the main cause of the presentation. Among the possible surgical options are balloon angioplasty, renal endarterectomy and nephrectomy. Our patient had a history of angioedema to ACE inhibitors. Even when the cross-reactivity of ARBs to ACE inhibitors was explained to him as $<$10%, he refused this option. In view of the non-functioning right kidney as evidenced by the split renal function scan, we decided to proceed with right nephrectomy. He responded extremely well as was seen post–nephrectomy, his renin and aldosterone levels dropped to normal range within 2 days of surgery. Similar encouraging results (hypertension, electrolyte abnormalities and proteinuria) after nephrectomy have been reported before in four similar patients [3, 6].

In conclusion, resistant hyponatremia and hypokalemia with nephrotic or non-nephrotic proteinuria could be a manifestation of HHS. Smoking cessation with ACE, ARB and rennin inhibitors (alone or in combination) should be tested. In those resistant to it or in whom they contraindicate, nephrectomy of the ischemic kidney can be done with excellent results.

Teaching points

(1) Hyponatremia and hypokalemia in the setting of hypertension warrants workup for an underlying hyperreninemic state.

(2) ACE, ARB and rennin inhibitors (alone or in combination) should be the first line of management along with smoking cessation.

(3) Definitive treatment involves alleviating the underlying cause of the hyperreninemic state.

Conflict of interest statement. None declared.

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