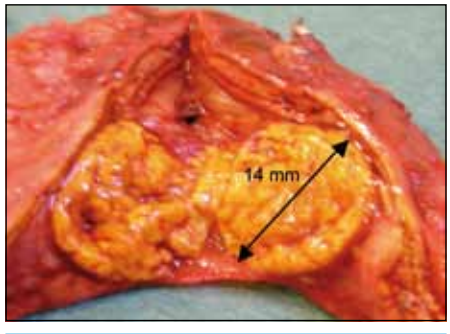
Conn's syndrome unmasked by thiazide-induced hypokalaemia

Discussion

This article presents two cases of Conn's syndrome in which hypokalaemia became apparent only on unopposed treatment with thiazide, or thiazide-like, diuretic. Readers are alerted to simple ways of increasing awareness of what is probably the commonest curable cause of hypertension, but two aspects are novel.

This article shows the first published case of positron emission tomography-computed tomography for lateralizing an adenoma. Second, the unmasking of hypokalaemia is not, as previously thought, just the result of enhanced Na+ delivery to the site of aldosterone action, since furosemide had no effect on plasma K+ in the patient in case 1. The most likely explanation is that the thiazide target, sodium–chloride cotransporter, has been shown to be an aldosterone-induced protein (Chiga et al, 2008). Therefore thiazide treatment in Conn's syndrome is a double whammy: inhibition of sodium–chloride cotransporter substantially increases Na+ delivery to the distal nephron, where its reabsorption in exchange for K+ is increased by aldosterone-induced upregulation of the epithelial Na+ channel.

Figure 1. Adrenalectomy specimen for case 1 showing a Conn's adenoma.



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Conclusions

Both cases highlight the importance of a suppressed plasma renin level (interpreted in the context of medication) in making the diagnosis of primary hyperaldosteronism (Hood et al, 2005). They also illustrate the benefit to patients of participation in clinical trials. After a decade or more of polypharmacy, it became possible to cure the younger patient and to reduce by about half the amount of therapy in the older. BJHM

Table 1. Effects of diuretic rotation on plasma electrolytes and renin

	Spironolactone	Furosemide	Amiloride	Bendroflumethiazide	Placebo
Renin (mU/litre)	5	6	2	5	2
Na+ (mM)	144	144	142	145	144
K+ (mM)	3.9	3.8	3.7	2.8	2.9

Table 2. Adrenal vein sampling result for case 1

	Aldosterone (pM)	Cortisol (nM)	Ratio (x1000)
Inferior vena cava	1546	276	5.6
Right adrenal vein	8160	5269	1.5
Left adrenal vein	54 800	1281	42.8

Case Report 1

A 33-year-old woman was diagnosed 12 years previously with hypertension (blood pressure 165/104 mmHg) and treated with nifedipine. She was a smoker with a history of asthma, taking salbutamol and beclometasone inhalers, with no significant family history of hypertension. In clinic she complained of fatigue, cramps, and intermittent left arm and face paraesthesia. Examination was unremarkable apart from grade II hypertensive changes on fundoscopy. Mean daytime ambulatory blood pressure was 141/91 mmHg. Initial investigations showed: Na+ 145 mM, K+ 4.2 mM, plasma renin mass <2 mU/litre (normal range (NR) 5–78 mU/litre), plasma aldosterone 278 pM (NR 100–450 pM) and 24-hour urinary sodium 79.2 mmol (NR 50–200 mmol). Her electrocardiogram was normal but echocardiogram revealed an elevated septal thickness at 1.11 cm. A computed tomography head scan and nerve conduction studies were normal.

She consented to a diuretic rotation study in 30 atypical young patients with low renin hypertension. The blinded, randomized study compared four diuretics. She drew the order spironolactone 50 mg, furosemide 20 mg, amiloride 20 mg, bendroflumethiazide 5 mg, placebo (*Table 1*). Unlike the other 29 patients, none of the diuretics reduced her blood pressure or de-suppressed her plasma renin level. On bendroflumethiazide, but not furosemide, she became hypokalaemic (K+ 2.8 mM) prompting a provisional diagnosis of Conn's syndrome on the basis that low-dose thiazides do not normally lower K+ below 3.4 mM, and lower levels should prompt a search for primary hyperaldosteronism. Magnetic resonance imaging showed a 10 mm x 13 mm adenoma in the left adrenal. Adrenal vein sampling confirmed lateralization of aldosterone secretion to the left side, with suppression of the contralateral adrenal (*Table 2*). Preoperatively, her blood pressure was well controlled at 134/86 mmHg by spironolactone 50 mg and amiloride 10 mg. This de-suppressed her plasma renin level (148 mU/litre) and unmasked an elevated plasma aldosterone level (2079 pM). The patient had a left adrenalectomy with histology suggesting an adrenocortical glomerulosa cell adenoma (*Figure 1*). Six weeks postoperatively she was asymptomatic with a blood pressure of 118/78 mmHg off medication. Two years later, her blood pressure remains <130/80 mmHg.

Case Report 2

A 48-year-old man had a 15-year history of poorly controlled hypertension. Because his systolic blood pressure remained >140 mmHg despite use of four drugs, he was referred from the authors' routine clinic for inclusion into PATHWAY-2 (a multicentre phase 4 study of optimal treatment of drug-resistant hypertension). He had been seen over 8 years by every clinical pharmacology consultant (five in total) in Addenbrooke's Hospital, Cambridge, and no cause for his hypertension identified. In 2004 his plasma renin level was 14 mU/litre and aldosterone level was 477 pM while being treated with lercanidipine, valsartan and bendroflumethiazide. Spironolactone was substituted for the thiazide in 2006, and initially brought his blood pressure down to less than 140/90 mmHg, prompting discharge from clinic. However, in early 2009 he was re-referred by his GP with readings up to 180/120 mmHg, despite increasing the spironolactone dose to 100 mg daily. A renin level of 14 mU/litre is relatively low for patients at stage 3 ('A+C+D') therapy, indicating a degree of Na+ retention, so chlortalidone was added. Following titration up to 50 mg, his blood pressure fell initially to 127/82 mmHg.

At screening for PATHWAY-2, gross, painful gynaecomastia (*Figure 2*) and normal plasma electrolytes (K+ 3.7 mM) were noted. The spironolactone was discontinued, while continuing his lercanidipine, lisinopril and chlortalidone. When he returned for his randomization visit 4 weeks later, he gave a 2-week history of proximal muscle weakness, and had a plasma K+ of just 1.9 mM, together with marked elevation of creatine kinase at 2041 U/litre (normal range 24–195 U/litre), suggesting a degree of hypokalaemia-associated rhabdomyolysis. He was admitted for an intravenous potassium infusion and as no extraneous cause of the hypokalaemia was apparent, it was attributed to the withdrawal from spironolactone and unmasking of probable Conn's syndrome by the unopposed thiazide-like (chlortalidone) therapy. Blood pressure was eventually controlled (137/85 mmHg) and normokalaemia restored (K+ 4.5 mM) by the stepwise addition of eplerenone 100 mg, amiloride 10 mg and chlortalidone 25 mg to his other drugs, lisinopril and lercanidipine.

An urgent computed tomography scan revealed a large right adrenal adenoma. Adrenal vein sampling showed lateralization of aldosterone secretion to the right (*Table 3*). The patient consented to a research 11C-metomidate positron emission tomography-computed tomography scan, which demonstrated increased uptake of metomidate into the right adrenal adenoma (standardized uptake value=30.5) compared to the contralateral normal left adrenal gland (standardized uptake value=11.6, *Figure 3*). The patient proceeded to a right adrenalectomy. On histological analysis, two nodules were seen on a background of adrenocortical hyperplasia (*Figure 4*). Three months postoperatively his blood pressure was well controlled at 131/82 mmHg on low doses of candesartan, lercanidipine and co-amilozide.

Figure 2. Gynaecomastia seen in case 2.

Table 3. Adrenal vein sampling result for case 2

	Aldosterone (pM)	Cortisol (nM)	Ratio (x1000)
High inferior vena cava	1988	768	2.58
Right adrenal vein	78800	7346	10.72
Left adrenal vein	48300	35305	1.36

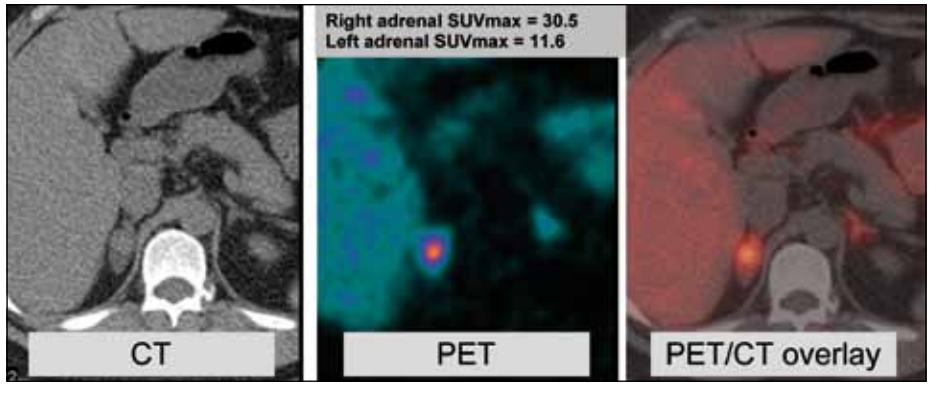

Figure 3. 11C-metomidate positron emission tomography-computed tomography (PET-CT) study for case 2. SUVmax = maximum standardized uptake value.

Figure 4. Adrenalectomy specimen for case 2 showing two adenomas.

LEARNING POINTS

- Conn's syndrome is probably the commonest curable cause of hypertension.
- This is the first published case of the use of positron emission tomography-computed tomography for lateralizing an adenoma.
- Unmasking hypokalaemia is not, as previously thought, just the result of enhanced sodium delivery to the site of aldosterone action.

Chiga M, Rai T, Yang SS, Ohta A, Takizawa T, Sasaki S, Uchida S (2008) Dietary salt regulates the phosphorylation of OSR1/SPAK kinases and the sodium chloride cotransporter through aldosterone. *Kidney Int* **74**(11): 1403–9

Hood S, Cannon J, Foo R, Brown M (2005) Prevalence of primary hyperaldosteronism assessed by aldosterone/renin ratio and spironolactone testing. *Clin Med* **5**(1): 55–60