Primary hyperaldosteronism due to adrenal microadenoma: a curable cause of refractory hypertension

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**Abstract**
The diagnosis of primary hyperaldosteronism due to microadenoma or unilateral adrenal hyperplasia can be challenging, since hypokalaemic alkalosis, high plasma aldosterone and a definite adenoma on imaging may all be absent.

**Method and result.** We describe three cases of resistant hypertension (on ≥ 5 antihypertensives) where hyperaldosteronism was suspected because of a suppressed plasma renin level despite treatment with multiple drugs which normally elevate renin. Renin mass was measured by a double-site chemi-immunoluminometric assay. All patients had normal plasma aldosterone levels. Hypokalaemia was present in the first two cases but computed tomography did not show clear-cut adenomas. Adrenal vein sampling (AVS) revealed lateralisation (＞4 times higher aldosterone to cortisol ratio (ACR) on the affected vs contra-lateral side). The third patient was normokalaemic and AVS showed only minimal lateralisation (ACR 1.3:1). The severe hypertension in all cases was reversed by adrenalectomy, with blood pressure falling to target despite withdrawal of all but one to two drugs. Use of aldosterone-renin ratio (ARR) was first introduced in 1981 and has become widely used in recent years as a screening test for primary hyperaldosteronism. However, it does not differentiate between adenoma and bilateral adrenal hyperplasia. In addition, the assay methods used for plasma renin and aldosterone vary and there is no uniform cut-off point used for further investigation such as adrenal imaging. The aim of this report is to illustrate the importance and difficulties of diagnosing microadenomas in patients with challenging hypertension, and to explain the ease and value of applying recent improvements in plasma renin assay.

**Methods and results**
This is a retrospective case series of three patients attending the hypertension clinic at Cambridge University NHS Foundation trust, who were found to have surgically reversible resistant hypertension. Individual cases are reported including initial presentation, investigation, management and outcome. All patients have given informed consent to this report.

**Introduction**
Primary hyperaldosteronism resulting from a Conn’s adenoma is one of the few potentially curable causes of hypertension. Several authors in recent years have suggested that it is more frequent than previously thought, accounting for more than 10% of arterial hypertension. Yet, curable adenomas continue to contribute only 1–2% to the total. Finding this group of patients can be difficult. Some clear-cut ‘macroadenomas’ are missed because of the absence of hypokalaemia, e.g. due to treatment with calcium-channel blockers, or because the decreased potassium is attributed to thiazide treatment. Here we describe three patients with either microadenomas or unilateral hyperplasia, where the clue was persistent suppression of plasma renin despite drugs which normally raise renin, computed tomography (CT) or magnetic resonance imaging (MRI) scans were equivocal or normal, and the critical investigation was adrenal vein sampling. All three patients had severe resistant hypertension that was reversed by adrenalectomy, with blood pressure (BP) falling to target despite withdrawal of all but one to two drugs. Use of aldosterone-renin ratio (ARR) was first introduced in 1981 and has become widely used in recent years as a screening test for primary hyperaldosteronism. However, it does not differentiate between adenoma and bilateral adrenal hyperplasia. In addition, the assay methods used for plasma renin and aldosterone vary and there is no uniform cut-off point used for further investigation such as adrenal imaging. The aim of this report is to illustrate the importance and difficulties of diagnosing microadenomas in patients with challenging hypertension, and to explain the ease and value of applying recent improvements in plasma renin assay.
24-hour-ambulatory BP monitoring and during hospitalisation despite receiving six antihypertensive drugs including spironolactone but not beta-blockade. Mild hypokalaemia (K+ > 3.2) also persisted. A CT scan was performed and showed normal adrenal glands (figure 1). Bilateral adrenal vein sampling (AVS) for cortisol and aldosterone assay showed an aldosterone:cortisol ratio (ACR) 2.5 times higher on the right than on the left. In the absence of an anatomical lesion on scanning, a ratio of 4:1 was considered the minimum to warrant surgery. Because of the persisting mild hypokalaemia, and completely suppressed renin despite receiving six drugs which normally elevate renin secretion, further investigations of the adrenal were performed. Although MRI scan of the adrenals was reported as normal initially, the coronal reconstruction revealed a possible 3 mm adenoma in the right adrenal (figure 2). Repeat adrenal vein sampling revealed an aldosterone:cortisol gradient of 11:1 between right and left (table 1). In discussion with the patient, potential benefit from adrenalectomy was considered to outweigh the risks of surgery. She underwent laparoscopic right adrenalectomy, which confirmed an adrenal nodule of 3 mm (figure 2). Because of the unpredictability of the response her treatment including spironolactone and amiloride were not initially discontinued, and post-operatively, her plasma Na+ fell transiently to 119 mmol/L. In the event, her BP fell rapidly, and at discharge was 130/80 mmHg. Six months later, she was on amlodipine 10 mg alone and her BP was 143/97 mmHg. Histology showed focal zona glomerulosa hyperplasia; the 3 mm adrenal nodule was a compact cell microadenoma (figure 3). Repeat renin and aldosterone levels were 9 mU/L and 175 pmol/L, respectively.

### Case 2

A 64-year-old man with 12 years history of hypertension and BP of 190/100 mmHg on three antihypertensives was referred to our clinic. Serum electrolytes were Na+ 147, K+ 3.2 and bicarbonate 32 mmol/L. The blood sample taken after normalising his K+ revealed a suppressed plasma renin of 2 mU/L but normal aldosterone

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**Table 1**

| Sampling site | Cortisol (nmol/L) | Aldosterone (pmol/L) | A/C ratio |
|---------------|------------------|----------------------|-----------|
| IVC           | 187              | 254                  | 1.32      |
| Right adrenal | 644              | 7,520                | 11.67     |
| Left adrenal  | 3,440            | 3,520                | 1.02      |

**Key:** Unilateral hypersecretion of aldosterone is demonstrated by the 11-fold difference in aldosterone/cortisol ratio between sides, and suppression of the ratio on the left to lower than the peripheral ratio in the IVC. A/C = aldosterone and cortisol ratio; IVC = inferior vena cava.

**Figure 1**

CT scan of patient 1 showing normal right and left adrenals. Note lack of intra-abdominal fat. CT = computed tomography.

**Figure 2**

MRI scan (a) and gross specimen (b) of patient 1. The 3 mm adenoma is arrowed in both panels. MRI = magnetic resonance imaging.
of 354 pmol/L. A CT scan of the adrenals was initially reported as normal, but subsequent review suggested a possible 7 mm nodule in the posterior limb of the right adrenal gland. He underwent bilateral adrenal vein sampling. This showed clear lateralisation to the right by a ratio of 116:1 (table 2). He underwent laparoscopic right adrenalectomy; and macroscopically there was a small adenoma of 3 mm but histology also revealed marked hyperplasia of the rest of the adrenal gland. Repeat renin and aldosterone levels were, respectively, 13 mU/L and < 100 pmol/L. At four months post operatively his BP was 115/80 mmHg on nifedipine 30 mg alone.

Case 3
A 56-year-old man was referred with a six-year history of hypertension that had become resistant to treatment. On five antihypertensive drugs, including spironolactone and an angiotensin (Ang) receptor blocker (ARB), his lowest BP was 193/116 mmHg. His electrolytes were Na⁺ 147, K⁺ 4.2, and bicarbonate 30 mmol/L. Renin was suppressed at 1 mU/L but his aldosterone was normal at 263 pmol/L. A CT scan of the adrenals reported a possible 6 mm left adrenal adenoma. On adrenal vein sampling, ACR was minimally lateralised to the right (1.3:1). MRI scan of the adrenals reported a possible right adrenal swelling of 6 mm. His BP fell progressively on the addition of amiloride 10–40 mg, to 154/93 mmHg. Because of the patient’s severe hypertension despite multiple drugs, the benefits of surgery were considered to outweigh the risk despite the remaining uncertainty about lateralisation. The right adrenal contained a 6 mm nodule (figure 3). Six months post-operatively his BP is 154/93 mmHg on treatment with bendroflumethiazide 2.5 mg plus candesartan 16 mg alone. Repeat plasma renin and aldosterone levels were 81 mU/L and 118 pmol/L, respectively.

Discussion
The advent of high-throughout robotic assay for renin mass has increased the availability of renin measurements, and extended the range of detectable concentrations compared to the more traditional renin activity assays. The latter rely on measurement of renin activity through the generation of Ang I during an hour’s incubation followed by measurement of this Ang I by radioimmunoassay. By contrast, measurement of renin mass is achieved through direct two-site immunoassay. In the case of fully automated immunoassays this is achieved by using a capture antibody bound to magnetic particles, and a detection antibody labelled with a chemiluminescent compound.4-7

Using the renin-mass assay, we were able to define a normal range in measurements on 850 randomly selected patients in primary care, excluding those on confounding drugs.3 Whereas the detection limit of the renin activity assay lay within the usually quoted normal range (i.e., the lower 5% of levels were undetectable) this is not the case for renin mass assay. This permits recognition of patients in whom renin secretion is suppressed below the normal range. In the same study we also found that a plasma renin suppressed despite blockade of the negative feedback of Ang II upon renin – by angiotensin-converting enzyme-inhibitors/ARB – was powerfully predictive of response to additional diuretic treatment.

The three cases reported here further illustrate how a suppressed plasma renin can be the only distinguishing feature of a Conn’s adenoma, and

| Table 2 |
| Adrenal vein sampling (patient 2). |

| Sampling site | Cortisol (nmol/L) | Aldosterone (pmol/L) | A/C ratio |
|---------------|------------------|----------------------|----------|
| IVC           | 219              | 484                  | 2.11     |
| Right adrenal | 908              | 59,040               | 65.02    |
| Left adrenal  | 1,597            | 903                  | 0.56     |

Key: A/C = aldosterone and cortisol ratio; IVC = inferior vena cava.
lead to diagnosis and cure when each of plasma K⁺, aldosterone and adrenal imaging have been normal. The existence of normokalaemic hyperaldosteronism is well documented, especially in patients receiving a calcium-channel blocker.⁶⁻⁹ However, we do not favour the recommendation to use aldosterone-renin ratio as the screening test for hyperaldosteronism. This ratio has a low specificity as it is elevated in all patients with a low plasma renin except those with rare monogenic syndromes, or liquorice excess. Hypokalaemia can usually be induced in primary hyperaldosteronism by administration of thiazide diuretic, which blocks the up-regulation of the Na⁺-Cl⁻ co-transporter by aldosterone and delivers more Na⁺ ions for exchange with K⁺ ions at the main site of aldosterone in the cortical collecting duct cells.

Our three cases suggest the possible value – as for some other endocrine glands – of distinguishing macroadenomas from microadenomas, in which plasma aldosterone may be normal and which may be difficult to visualise even with the best CT/MRI imaging.⁶⁻¹¹ However, we cannot be certain that all of the microadenomas were functional, and some of our patients fit previous descriptions of unilateral adrenal hyperplasia.⁸⁻¹² A further possibility is that especially in our third patient where lateralisation was marginal – is that there is a non-linear increase in mineralocorticoid response with increased aldosterone secretion, so that debulking might be effective whenever adrenal is removed. Because of the severity of hypertension in this patient, and the likelihood that aldosterone was contributing to the renin-suppression, we feel that total suppression surgery could be calculated in favour of proceeding.

The other two patients are, however, more secure paradigms, and illustrate the power of selective adrenal vein sampling. In order to achieve > 95% success with this technique, there are several requirements. The physician must ensure that the contralateral adrenal has not been 'de-suppressed' by spironolactone or amiloride; since the severity of hypertension may preclude complete withdrawal of these drugs, we empirically check that plasma renin is < 25 mU/L before sampling. The exaggerated diurnal rhythm of aldosterone secretion from adenomas suggests that sampling is better conducted early in the day. The radiologist should be prepared to search for the right adrenal vein, and take multiple samples from candidate veins draining directly into the IVC. Imaging of the vein by CT/MRI can help provide exact co-ordinates. Sampling might need repeating in our first case if diagnosis is still in question and there is difficulty in managing hypertension.

In conclusion, we present three patients with aldosterone-secreting microadenomas of the adrenal, who were suspected from their suppressed plasma renin, and confirmed by lateralisation of aldosterone-cortisol ratio on adrenal vein sampling. Despite only modest falls in BP on spironolactone and/or amiloride, all three patients had sustained drops of at least 50 mmHg systolic after removal of tumour, accompanied by a reduction in the number of drugs from 5–6 to 1–2.

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