Endocrinology, Diabetes & Metabolism CASE REPORTS

R Goupil and others | Use of plasma metanephrine in AVS

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Use of plasma metanephrine to aid adrenal venous sampling in combined aldosterone and cortisol over-secretion

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Summary

In patients with primary aldosteronism (PA) undergoing adrenal venous sampling (AVS), cortisol levels are measured to assess lateralization of aldosterone overproduction. Concomitant adrenal autonomous cortisol and aldosterone secretion therefore have the potential to confound AVS results. We describe a case where metanephrine was measured during AVS to successfully circumvent this problem. A 55-year-old hypertensive male had raised plasma aldosterone/renin ratios and PA confirmed by fludrocortisone suppression testing. Failure of plasma cortisol to suppress overnight following dexamethasone and persistently suppressed corticotrophin were consistent with adrenal hypercortisolism. On AVS, comparison of adrenal and peripheral A/F ratios (left 5.7 vs peripheral 1.0; right 1.7 vs peripheral 1.1) suggested bilateral aldosterone production, with the left gland dominant but without contralateral suppression. However, using aldosterone/metanephrine ratios (left 9.7 vs peripheral 2.4; right 1.3 vs peripheral 2.5), aldosterone production lateralized to the left with good contralateral suppression. The patient underwent left laparoscopic adrenalectomy with peri-operative glucocorticoid supplementation to prevent adrenal insufficiency. Pathological examination revealed adrenal cortical adenomas producing both cortisol and aldosterone within a background of aldosterone-producing cell clusters. Hypertension improved and cured of PA and hypercortisolism were confirmed by negative post-operative fludrocortisone suppression and overnight 1 mg dexamethasone suppression testing. Routine dexamethasone suppression testing in patients with PA permits detection of concurrent hypercortisolism which can confound AVS results and cause unilateral PA to be misdiagnosed as bilateral with patients thereby denied potentially curative surgical treatment. In such patients, measurement of plasma metanephrine during AVS may overcome this issue.

Learning points:

- Simultaneous autonomous overproduction of cortisol and aldosterone is increasingly recognised although still apparently uncommon.
- Because cortisol levels are used during AVS to correct for differences in dilution of adrenal with non-adrenal venous blood when assessing for lateralisation, unilateral cortisol overproduction with contralateral suppression could confound the interpretation of AVS results
- Measuring plasma metanephrine during AVS to calculate lateralisation ratios may circumvent this problem.

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Background

Primary aldosteronism (PA) is a potentially curable form of hypertension due to autonomous adrenal production of aldosterone. Once PA is confirmed by the demonstration of non-suppressible aldosterone production, differentiation of unilateral from bilateral PA facilitates selection of optimal treatment. Because imaging is unreliable in this respect, adrenal venous sampling (AVS) is recommended in all patients with PA who are potential candidates for adrenalectomy (1).

Simultaneous autonomous overproduction of cortisol and aldosterone is increasingly recognised although still apparently uncommon (2). Because cortisol levels are used during AVS to correct for differences in dilution of adrenal with non-adrenal venous blood when assessing for lateralisation, unilateral cortisol overproduction with contralateral suppression could confound the interpretation of AVS results (3). Although the utility of measuring plasma metanephrine during AVS for the assessment of successful cannulation has been previously demonstrated (4), data are lacking as to its use in assessing lateralisation. We describe herein a case which illustrates how plasma metanephrine levels can be measured during AVS and used in lateralisation indices to circumvent the potential difficulties in correctly interpreting AVS results imposed by concomitant autonomous aldosterone and cortisol hypersecretion.

Case presentation

A 55-year-old man was referred for investigation of hypertension of two years duration which was uncontrolled despite treatment with an angiotensin-receptor blocker and a calcium-channel blocker. The patient denied symptoms suggestive of secondary causes of hypertension or hypercortisolism. Apart from an elevated blood pressure (183/131 mmHg), physical examination was unremarkable. Four weeks after conversion of his medications to non-interfering antihypertensive drugs (verapamil slow-release, hydralazine and prazosin), a detailed diagnostic workup was undertaken.

Investigation

Ambulatory blood pressure monitoring revealed an average 24 h blood pressure of 164/97 mmHg. Plasma sodium was 141 mmol/l, potassium 3.4 mmol/l, creatinine 63 umol/l and fasting blood glucose 5.2 mmol/l. The hypokalemia normalised with potassium supplements. Investigations showed minimal evidence of end-organ damage (left ventricular mass index 100 g/m^2, no microalbuminuria). Renal artery stenosis was excluded by renal artery duplex ultrasound. A contrast-enhanced CT scan of the adrenal glands demonstrated two nodules in the left adrenal body measuring 1.5×1.5 cm and 1.0×1.4 cm with a normal appearing right gland. Investigation revealed an elevated aldosterone/renin ratio (aldosterone 340 pmol/l, renin concentration <2 mU/l, ratio >170 (normal <70)) and a non-suppressible cortisol during a 1 mg overnight dexamethasone suppression test (ODST; basal 380 nmol/l, post 150 nmol/l (normal <70)). PA was confirmed by fludrocortisone suppression testing (day 4 upright plasma aldosterone 570 pmol/l (normal <165)) (5). ACTH-independent autonomous cortisol secretion was confirmed with a 3 mg ODST which failed to suppress cortisol (basal 370 nmol/l, post 180 nmol/l) while suppressing ACTH (from 8 ng/l to <5 ng/l). Plasma free and 24 h urinary metanephrines were normal.

AVS was performed without ACTH-stimulation to assess lateralisation of aldosterone production in accordance with our centre's standard practice. Since the presence of a unilateral adrenal lesion producing both aldosterone and cortisol was possible, there were concerns that the results of the AVS could be confounded, with overproduction of cortisol potentially lowering the aldosterone/cortisol (A/F) ratio on the side of the lesion while increasing it on the opposite side due to contralateral cortisol suppression, thereby resulting in a misdiagnosis. To circumvent this issue, plasma metanephrine was measured concomitantly to cortisol and aldosterone in AVS samples. By our usual criteria, AVS is considered to show lateralization when i) the A/F ratio on the affected side is at least twice the peripheral ratio and ii) the contralateral A/F ratio is similar to or lower than peripheral (contralateral suppression). As shown in Table 1, AVS failed to show lateralization with cortisol as the denominator, appearing to show the left adrenal to be dominant but without contralateral suppression, suggesting bilateral PA. In contrast, with metanephrine as the denominator, aldosterone production clearly lateralized to the left with good contralateral suppression. Moreover, the left adrenal vein cortisol/metanephrine ratio was more than twice the right ratio (1.7 vs 0.8), suggestive of a left adrenal source of hypercortisolism.

Treatment

In view of these findings, the patient underwent a left laparoscopic adrenalectomy with perioperative hydrocortisone supplementation followed by several weeks of cortisone acetate (with doses gradually reducing to zero).

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Table 1 Results from adrenal venous sampling.

Sample	Aldosterone	Cortisol	Aldosterone/ Cortisol ratio	Metanephrine	Aldosterone/ Metanephrine ratio
Left adrenal vein	168 970	29 797	5.7	17 500	9.7
Peripheral	582	607	1.0	243	2.4
Right adrenal vein	45 982	26 624	1.7	34 500	1.3
Peripheral	720	662	1.1	283	2.5

Units: Aldosterone (pmol/l); Cortisol (nmol/l); Metanephrine (pmol/l).

Macroscopically, the adrenal gland was composed of a large adenoma within an enlarged multinodular gland (Fig. 1A). Pathology showed an adrenal cortical adenoma composed of large cells with granular eosinophilic cytoplasm containing fine brown pigment. Immunohistochemistry was performed to identify which nodules were secreting cortisol and aldosterone following a previously published protocol (6).

The largest nodule (Fig. 1B) and the two smaller ones (Fig. 1C) strongly stained with antibodies directed against 11β-hydroxylase (CYP11B1), 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17α-hydroxylase (CYP17) with only minimal staining for aldosterone synthase (CYP11B2), consistent with lesions producing abundant cortisol but possibly also small amounts of aldosterone. In other areas of the adrenal gland, however, strongly CYP11B2-positive cell clusters were seen (Fig. 2), and presumably represented the source of aldosterone excess (6). Since the CYP11B2-positive cluster shown in Fig. 2A, panel 1 appeared not to be subcapsular, it might be better termed an aldosterone-producing micronodule rather than an APCC.

Outcome and follow-up

By 4 months post-operation, hypertension improved and potassium normalized. Biochemical cure of PA and hypercortisolism were confirmed by negative fludrocortisone suppression testing (day 4 aldosterone 120 pmol/l) and ODST (basal cortisol 230 nmol, post 20 nmol/l).

Discussion

The prevalence of combined PA and autonomous adrenal cortisol production is difficult to establish, as not all PA patients are evaluated for hypercortisolism. Rates up to 21% among PA patients have been reported (2), although in our experience (unpublished data), it is below 5% despite routine ODST in all. Since post-operative adrenal insufficiency can be avoided by identification of hypercortisolism and peri-operative administration of corticosteroid supplementation, it could be argued that cortisol production should be assessed in all patients with PA (7).

AVS is the most reliable means of identifying surgically-correctable subtypes of PA (1). The measurement of cortisol in collected samples allows the determination of successful adrenal venous cannulations, and correction of aldosterone levels for differences in dilution of adrenal with non-adrenal blood. Cortisol has a variable secretion pattern and a long half-life, which can reduce the difference between peripheral and adrenal vein levels and hinder catheter placement assessment (selectivity) during AVS. To address this problem, ACTH-stimulation prior to AVS can be used to increase cortisol production, but it amplifies the cost and complexity of the procedure. Moreover, there is currently no agreement in regard to the most appropriate diagnostic criteria to determine successful cannulation and lateralisation (8). With concomitant cortisol overproduction, there is a risk of misinterpreting AVS. An increased level of cortisol from one adrenal gland can falsely lower the corresponding A/F ratio while contralateral suppression of cortisol increases the ratio on the opposite side (3). This can incorrectly classify patients as having bilateral aldosterone overproduction and deny them the opportunity for a surgical cure. In the patient described herein, concurrent production of aldosterone and cortisol led to false loss of lateralization on AVS which was rectified when metanephrine levels were used to correct aldosterone levels. Even though his adrenal venous aldosterone/cortisol ratios were higher on the left side than the right, the lack of contralateral suppression meant that he failed to fulfil our criteria for lateralization, and we have recently reported contralateral suppression to be an important predictor of clinical outcome in patients who undergo unilateral adrenalectomy (9). Therefore, had sole reliance been placed on the AVS cortisol levels, it is likely that he would have been treated medically rather than undergo unilateral adrenalectomy, which led to the cure of both his PA and hypercortisolism. While demonstration of

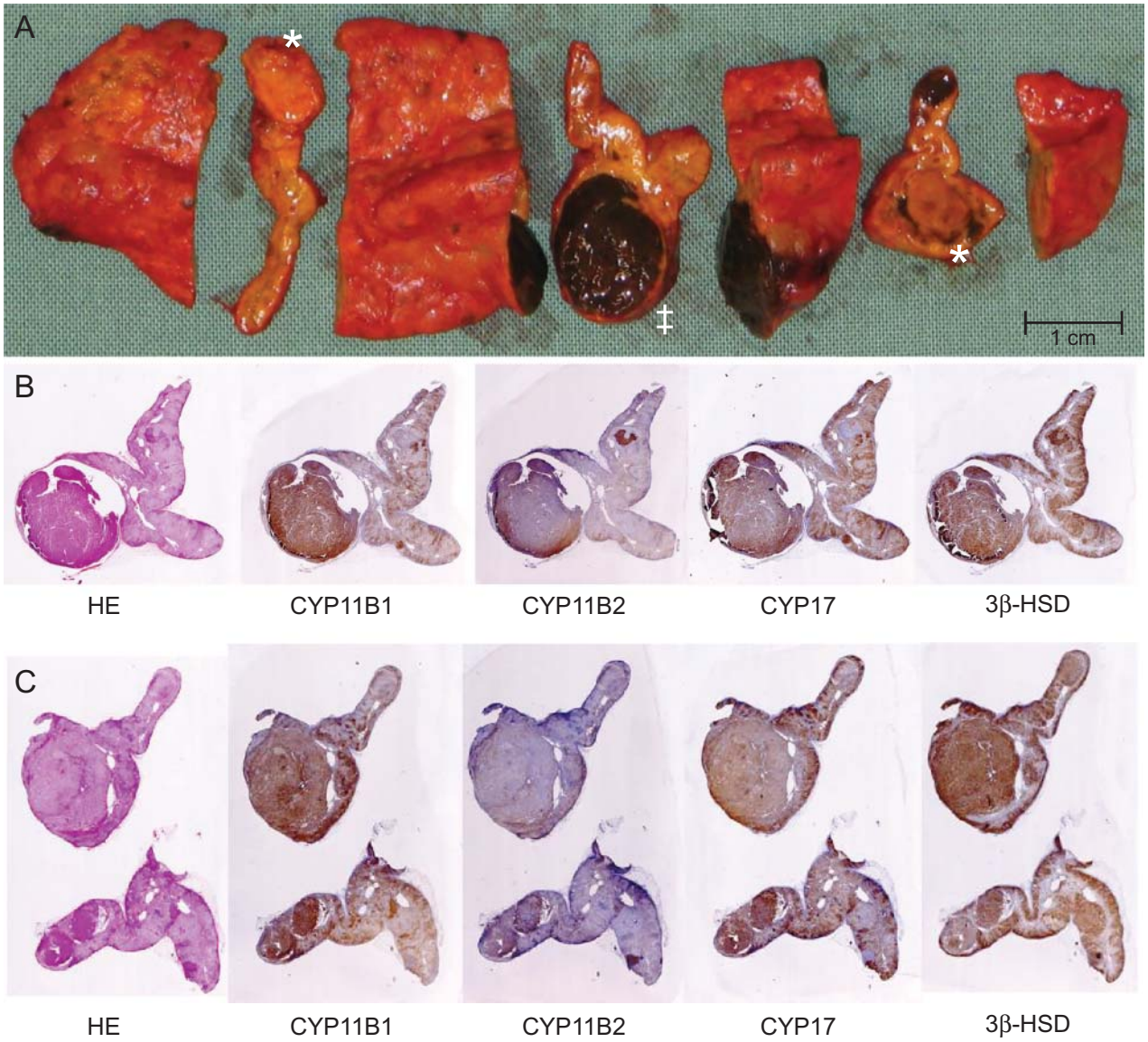

Figure 1

Pathology of adrenalectomy specimen. (A) Macroscopic pathology showing large adenoma (‡) and two smaller nodules (*). (B) Immunohistochemistry of the large adenoma. (C) Immunohistochemistry of the two smaller nodules. HE, Hematoxylin and eosin stain; CYP11B1, 11β-hydroxylase stain; CYP11B2, aldosterone synthase stain; 3β-HSD, 3β-hydroxysteroid dehydrogenase stain; CYP17, 17α-hydroxylase stain.

ACTH-independent hypercortisolism with a nodular adrenal gland on CT might be considered sufficient to warrant unilateral surgery, it remains reasonable to consider non-surgical management of subclinical Cushing's syndrome (10).

Epinephrine measurements have been successfully used to evaluate selectivity and lateralisation. There are, however, concerns about its high fluctuations and high levels of variation between individuals. Metanephrine has a short circulation half-life and is released constantly by the adrenal glands, resulting in very high differences between adrenal and peripheral venous levels. The use of metanephrine has recently been studied as a substitute to cortisol to evaluate success of adrenal venous cannulation during AVS (4). In that prospective study, plasma metanephrine was reported to be superior to cortisol in unstimulated AVS and similar in ACTH-stimulated AVS. To our knowledge, there are no previous reports regarding the use of plasma metanephrine to evaluate lateralisation of aldosterone production in PA. This case report

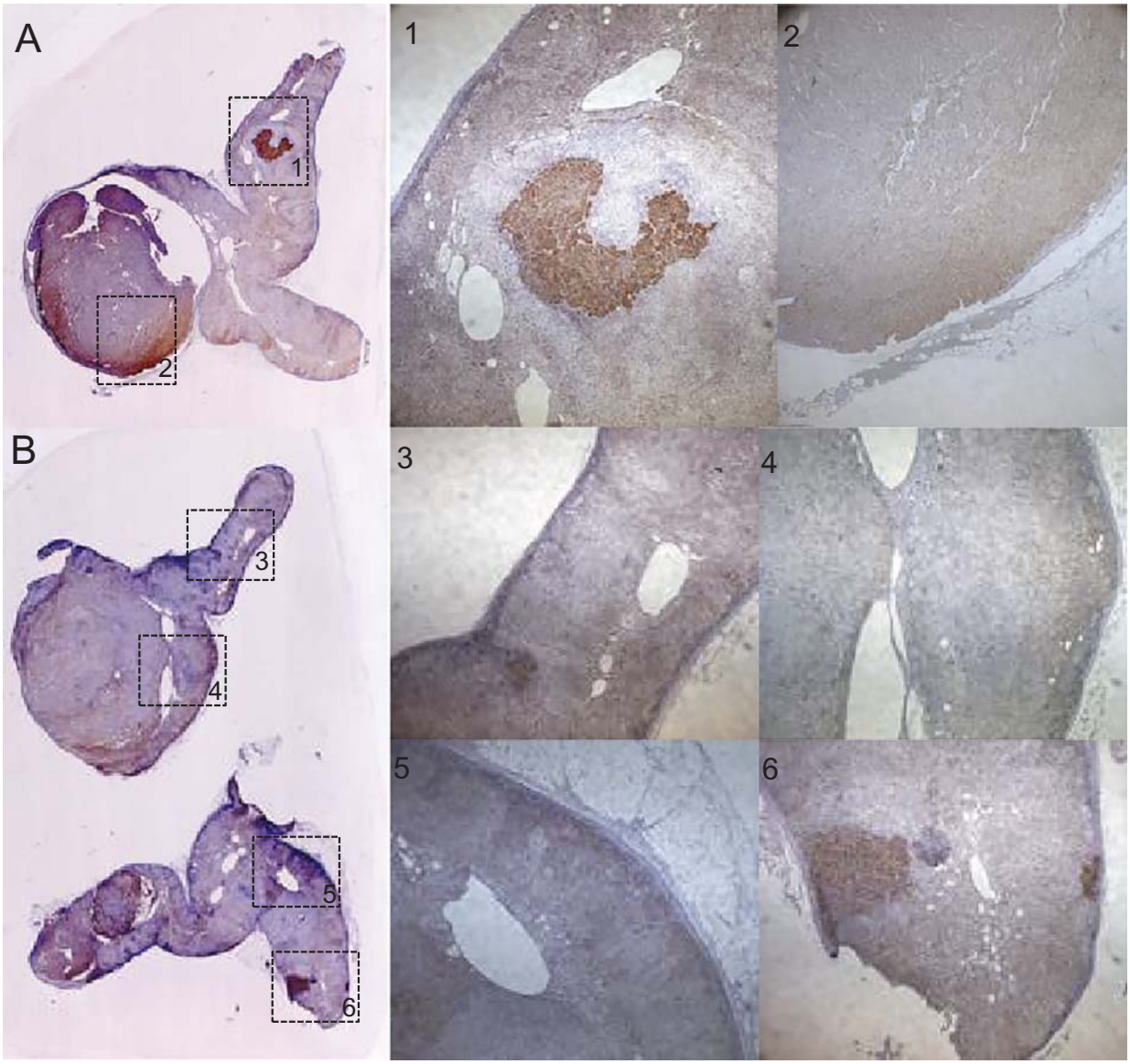

Figure 2

Immunohistochemistry with aldosterone synthase (CYP11B2) stain. Higher magnification showing clusters of positively staining (hence presumably aldosterone-producing) cells (indicated by arrows) in adrenal cortex adjacent to the large adenoma (A) and the two smaller nodules (B).

illustrates how using aldosterone to metanephrine ratios during AVS can help correctly differentiate between unilateral and bilateral PA when concomitant hypercortisolism is present.

Although suggestive, it would be premature to conclude from this single report that metanephrine measurement will consistently prove to be useful to prevent misinterpretation of AVS in adrenocortical lesions co-secreting cortisol and aldosterone. Theoretical reasons why this may not be the case include: i) adrenal blood flow is centripetally directed and the adrenal medulla is thus under the influence of cortisol released by adrenocortical cells; and ii) glucocorticoids stimulate catecholamine synthesis and secretion from adrenomedullary chromaffin cells. It is thus conceivable that local production of metanephrine may be increased in cortisol-secreting lesions. Lastly, whether the procedure would be equally useful in AVS with ACTH-stimulation remains to be determined. Prospective studies are justified to address this interesting issue.

While AVS studies should be performed in all eligible PA patients seeking the possibility of surgical resolution, concomitant autonomous adrenal cortisol

overproduction can lead to erroneous interpretation of AVS and deprive the patient of a surgical cure. This case report is possibly the first to illustrate how measuring plasma metanephrine during AVS may circumvent this problem, and demonstrates the need of prospective studies to further examine this alternative.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written consent for publication of this case report was obtained from the patient.

Author contribution statement
R Goupil performed data collection and manuscript preparation. M Wolley performed manuscript revision. J Ungerer and B McWhinney performed metanephrine measurements and manuscript revision. K Mukai performed immunohistochemistry and manuscript revision. M Naruse performed immunohistochemistry interpretation as well as manuscript revision. R D Gordon performed manuscript preparation and revision. M Stowasser, the named physician of the patient, performed manuscript preparation and revision.

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