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Endocrinology, Diabetes & Metabolism CASE REPORTS

L M Angus and others | Hypoaldosteronism post-adrenalectomy

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Persistent hypoaldosteronism post-adrenalectomy for primary aldosteronism – a role for pre-operative spironolactone?

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Summary

Primary aldosteronism is one of the most common (affecting up to 10%) yet treatable causes of hypertension in our community, notable due to an associated elevated risk of atrial fibrillation, stroke and myocardial infarction compared to essential hypertension. Guidelines have focussed on improving case detection due to significant underdiagnosis in the community. While our case experienced significant delay in diagnosis, we highlight a state of protracted, persistent post-operative hypoaldosteronism which manifested with severe hyponatraemia and hyperkalaemia, necessitating long-term mineralocorticoid replacement. We discuss whether pre-operative mineralocorticoid receptor antagonists to stimulate aldosterone secretion from the contralateral gland may have prevented this complication.

Learning points:

- Hypoaldosteronism is an uncommon complication of adrenalectomy for primary aldosteronism, typically manifesting with hyperkalaemia and hyponatraemia. While most cases are transient, it may be persistent, necessitating ongoing mineralocorticoid replacement.
- Routine electrolyte monitoring is recommended post-adrenalectomy.
- Risk factors for hypoaldosteronism include age >50 years, duration of hypertension >10 years, pre-existing renal impairment and adrenal adenoma size >2 cm.
- Mineralocorticoid receptor antagonists may assist in the management of hypokalaemia and hypertension pre-operatively. However, it is unclear whether this reduces the risk of post-operative hypoaldosteronism.

Background

This case highlights an uncommon but potentially life threatening complication of adrenalectomy for primary aldosteronism.

Case presentation

A 76-year-old man was referred to Endocrinology Clinic with a 25-year history of treatment-refractory hypertension and suspected primary aldosteronism. Notably, he had a history of thiazide diuretic-induced hypokalaemia and suboptimal blood pressure control despite four anti-hypertensive medications including olmesartan, atenolol, prazosin and moxonidine. Following the discontinuation of interfering anti-hypertensives (atenolol and olmesartan), commencement of verapamil and uptitration of prazosin and moxonidine, the patient's seated blood pressure was 135/80 mmHg and serum potassium was 3.8 mmol/L

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(3.5–5.2mmol/L),withoutanypotassiumsupplementation. A seated saline suppression test confirmed the diagnosis of primary aldosteronism, with a baseline plasma aldosterone concentration (PAC) of 533 pmol/L (100–950 pmol/L erect), direct renin concentration of 1.1 mU/L (3.3–4.1 mU/L erect) and aldosterone renin ratio of 490 (<70), and plasma aldosterone concentration of 290 pmol/L 4 h following the administration of 2 L 0.9% sodium chloride solution (normal response: <170 pmol/L). A dedicated adrenal CT scan demonstrated a left adrenal adenoma measuring 12 × 7 mm with absolute contrast washout of 83.6%, while the right adrenal gland was normal in size, shape and enhancement characteristics with no discrete lesion. However, adrenal vein sampling demonstrated right-sided lateralisation (bilateral simultaneous adrenal vein sampling, pre-adrenocorticotrophic hormone (ACTH) infusion: right adrenal vein aldosterone cortisol ratio to left adrenal vein aldosterone cortisol ratio 47.9; both adrenal veins were successfully cannulated with left and right adrenal vein to peripheral vein cortisol ratio >2). Laparoscopic right adrenalectomy was performed 8 weeks later with histology consistent with a benign adrenocortical adenoma measuring 4 mm in maximum diameter. A mineralocorticoid receptor antagonist was not introduced prior to surgery.

On day 1 post-adrenalectomy, the patient's serum sodium was 133 mmol/L (135–145 mmol/L), serum potassium 3.8 mmol/L (3.5–5.2 mmol/L) and blood pressure up to 170/90 mmHg. The patient was discharged on moxonidine with a plan to reintroduce additional anti-hypertensives if required.

The endocrine surgery team reviewed the patient 1 week post-operatively, noting ambulatory systolic blood pressure measurements up to 150 mmHg, and moxonidine was changed to verapamil modified release 240 mg daily but no electrolyte monitoring was performed. The reasons for this change of therapy are not documented. The endocrinology team reviewed the patient 12 weeks post-operatively, with a recorded blood pressure of 136/76 mmHg on verapamil modified release 240 mg daily. Assessment of serum electrolytes at this time revealed severe hyponatraemia (serum Na^+: 124 mmol/L) and mild hyperkalaemia (serum K^+:5. 7 mmol/L). Due to initial concern of glucocorticoid and mineralocorticoid deficiency, hydrocortisone 10 mg twice daily and fludrocortisone 50 µg daily were commenced, while other investigations were arranged. Subsequent investigation was consistent with isolated mineralocorticoid deficiency with low plasma aldosterone (74 pmol/L), inappropriately normal renin (27 mU/L) and a normal cortisol response to ACTH (peak cortisol: 667 nmol/L at 60 min following administration of ACTH). Hydrocortisone was ceased and fludrocortisone 50 µg daily was continued with subsequent normalisation of serum sodium (139 mmol/L) and potassium (4.9 mmol/L).

Five months post-adrenalectomy (2 months following the initiation of fludrocortisone), fludrocortisone was ceased with the intention of promoting stimulation of renin and production of aldosterone by the remaining zona glomerulosa cells. However, this resulted in moderate to severe hyponatraemia (nadir serum sodium 121 mmol/L) and after 3 months of persistent hyponatraemia without a significant improvement in PAC (peak 181 pmol/L), fludrocortisone was reintroduced initially at 25 µg daily and subsequently uptitrated to 150 µg daily with improvement and normalisation of serum sodium. Mineralocorticoid replacement will be continued indefinitely given persistent hypoaldosteronism post-adrenalectomy.

Investigation

Key test results and events are presented in Table 1.

Treatment

The patient was commenced on oral fludrocortisone to treat isolated mineralocorticoid deficiency post-adrenalectomy for primary aldosteronism. Attempts were made to wean and cease fludrocortisone, aiming to achieve stimulation of renin and ultimately aldosterone production from the remaining adrenal gland. However, after 3 months of persistent and significant hyponatraemia, fludrocortisone was reintroduced and uptitrated to a dose of 150 µg daily with the aim of achieving a normal serum sodium and potassium level.

Outcome and follow-up

The patient was last reviewed on 29 June 2021 (15 months post-adrenalectomy). Current therapy includes fludrocortisone 150 µg daily and amlodipine 10 mg daily. Average home blood pressure recordings were approximately 140/80 mmHg and the most recent serum electrolytes on 16 June 2021 showed normal serum sodium (serum Na^+ 135 mmol/L) and potassium (serum K^+ 5.1 mmol/L). This represents a significant improvement in blood pressure and need for anti-hypertensive therapy post-adrenalectomy for primary aldosteronism, but a persistent need for fludrocortisone due to the uncommon complication of permanent hypoaldosteronism. We hypothesise that the persistent need for anti-hypertensive

Table 1 Key test results and events. Bold values reflect test results outside the quoted normal reference range.

Test	Reference range	2019	2020						2021	
		15/10	11/3	4/6	18/6	10/8	13/11	23/11	21/12	18/1	16/6
Sodium, mmol/L	135–145	140	**133**	**124**	139	138	**121**	**123**	**127**	**132**	135
Potassium, mmol/L	3.5–5.5	4.3	3.8	**5.7**	4.9	5.2	5.4	4.8	**5.7**	5.5	5.1
Urea, mmol/L	3.5–9.5	6.9	8.0	9.1	7.3	9.4	9.2	6.5	6.1	6.3	6.1
Creatinine, µmol/L	60–115	75	76	90	80	88	91	84	80	78	84
eGFR, mL/min/1.73m^2	>60	85	85	71	83	73	70	78	83	83	77
Aldosterone, pmol/L erect	100–950			**74**	**<50**	128		181	126	110	83
Renin, mU/L erect	3.3–41			27	**5.0**	12		18	9.1	4.4	2.4
ARR	<70			3	<10	11		10	14	25	35
Fludrocortisone dose, µg daily		0	0	0	50	0	0	25	50	100	150
Events											
11 March 20	Day 1 post-right adrenalectomy										
9 June 20	Hyponatraemia and hyperkalaemia detected, 12 weeks post-adrenalectomy. Hydrocortisone 10mg bd and fludrocortisone 50 µg daily commenced										
16 June 20	ACTH stimulation test demonstrated normal cortisol response (662 nmol/L at 60 min)										
23 June 20	Hydrocortisone ceased and fludrocortisone continued										
4 August 20	Fludrocortisone ceased in attempt to stimulate renin and aldosterone production										
13 November 20	Fludrocortisone restarted 25 µg daily due to persistent and significant hyponatraemia										
26 November 20	Fludrocortisone increased 50 µg daily due to persistent hyponatraemia										
23 December 20	Fludrocortisone increased 100 µg daily due to persistent hyponatraemia										
16 February 21	Fludrocortisone increased to 150 µg daily due to persistent hyponatraemia										

therapy reflects co-existing essential hypertension given primary aldosteronism has been cured.

Discussion

Correlation between imaging and adrenal vein sampling

The diagnostic algorithm for primary aldosteronism involves screening, confirmatory testing and localisation studies to distinguish unilateral pathology which may be amenable to adrenalectomy from bilateral adrenal hyperplasia. Current Endocrine Society guidelines recommend dedicated adrenal imaging for all cases of primary aldosteronism and adrenal vein sampling in most cases to assist with localisation due to poor correlation between CT and adrenal vein sampling as highlighted by our patient (1). In fact, a review of 950 patients who underwent both CT/MRI and adrenal vein sampling showed only 62.2% concordance (2).

Post-operative hypoaldosteronism

Post-operative hyperkalaemia is an uncommon and usually transient phenomenon following adrenalectomy for primary aldosteronism, attributed to suppression of renin and therefore reduced aldosterone production from the contralateral adrenal gland (3). It has been proposed that chronic suppression of renin may cause atrophy of the zona glomerulosa cells and hypoaldosteronism, analogous to atrophy of the zona fasciculata cells and hypocortisolism observed in some patients with Cushing's syndrome due to chronic suppression of corticotrophin releasing hormone (CRH) and ACTH (3). The additional regulators of aldosterone secretion – namely ACTH and potassium – may explain why post-operative hyperkalaemia and hypoaldosteronism do not occur more commonly in patients with surgically treated primary aldosteronism (3). It has been speculated that injury to the juxtaglomerular apparatus from long-standing primary aldosteronism may account for rare cases of hyporeninaemic hypoaldosteronism post-adrenalectomy (3), though we could not find any references that demonstrate juxtaglomerular damage in this setting.

Previously identified risk factors include age >50 years, duration of hypertension >10 years, pre-existing renal impairment, adrenal adenoma size >2 cm (3, 4) and a contralateral suppression index <0.47 (calculated by dividing the aldosterone cortisol ratio of the non-dominant adrenal vein by the external iliac vein) (5). Identified risk factors in our case included patient age, duration of hypertension and a contralateral suppression index of 0.23. However, despite a presumed long duration of primary aldosteronism, the patient's renal function was not significantly impaired and the identified right adrenal adenoma measured only 4 mm, which are not in keeping with risk factors identified by Park *et al.* (4). Post-

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operative microalbuminuria has also been associated with post-operative hyperkalaemia (3), but this result was not requested in our case.

In our case, adrenalectomy and cure of primary aldosteronism resulted in a significant decrease in the number of anti-hypertensive medications required for adequate blood pressure control. The persistent need for anti-hypertensive therapy may reflect co-existing essential hypertension. Additionally, the seemingly predominant effect of hypoaldosteronism on electrolyte balance rather than blood pressure may reflect additional regulatory mechanisms such as alterations in cardiac output and peripheral vascular resistance.

Role of pre-operative mineralocorticoid receptor antagonists

In light of the hypothesis that chronic suppression of renin may cause atrophy of zona glomerulosa cells, the use of pre-operative mineralocorticoid receptor antagonists to stimulate renin has been suggested to decrease the risk of hypoaldosteronism post-adrenalectomy. Several retrospective observational studies have failed to demonstrate a significant difference in rates of post-operative hyperkalaemia using this approach. However, while Fischer *et al.* (3) prescribed mineralocorticoid receptor antagonists to most patients (78%) pre-operatively, the duration of treatment was variable (range 1–7 months) and pre-operative renin levels remained suppressed (median renin 2.7 and 2.9 mU/L in those with transient and persistent hyperkalaemia respectively). Similarly, pre-operative mineralocorticoid receptor antagonists were prescribed to most patients (75.7%) by Park *et al.* (4), but pre-operative renin remained suppressed (median plasma renin activity 0.15 and 0.10 ng/mL/h in those with transient and persistent hyperkalaemia respectively) (3, 4). It is possible that titration of mineralocorticoid receptor antagonist therapy to achieve a non-suppressed renin pre-operatively would have reduced the risk of post-operative hyperkalaemia and hypoaldosteronism in our patient. However, if persistent hypoaldosteronism is predominantly caused by irreversible damage to the juxtaglomerular apparatus and production of renin, this approach would not be expected to be successful. Further studies are warranted.

Our case provides a pertinent example of persistent hypoaldosteronism following adrenalectomy for long-standing primary aldosteronism. In addition, the discordant CT and adrenal vein sampling findings exemplify the importance of adrenal vein sampling. Clinicians should be aware of the risk of post-operative hypoaldosteronism and hyperkalaemia following adrenalectomy and routinely measure electrolytes within the initial period post-adrenalectomy. Pre-operative mineralocorticoid receptor antagonist therapy to stimulate renin secretion from the contralateral gland may improve control of blood pressure and hypokalaemia, but further research is needed to assess whether this reduces the risk of post-operative hypoaldosteronism.

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 has been obtained from the patient.

Author contribution statement
L M A contributed to conception, drafting, revision and final approval. J Y and A S C contributed to conception, revision, and final approval of work. A S C was the main physician responsible for the patient's care. All authors agree to be accountable for all aspects of the work and contributed significantly.

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