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Approach to a Patient with Suspected Primary Aldosteronism

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ABSTRACT

A typical case of a patient with suspected mineralocorticoid hypertension is discussed. The presentation follows sequential steps through the diagnostic evaluation and treatment of primary aldosteronism. The diagnostic approach can be classified into three phases: screening tests, confirmatory tests, and subtype differentiation studies. It is essential to follow the evaluation steps to elucidate the cause of primary aldosteronism, as this determines the appropriate treatment. Another lesson to learn is the need to critically appraise the value of any endocrine test, particularly if it is likely to influence the management strategy in an individual patient.

Keywords: Conn's syndrome, hypokalaemia, mineralocorticoid hypertension, primary aldosteronism

CASE DISCUSSION

History: A 57-year-old woman with a long-standing history of hypertension was referred for investigation of hypokalaemia. On review, she has been diagnosed with hypertension for 10 years and she was under treatment and follow-up by her family physician. Her blood pressure was adequately controlled with nifedipine 10 mg three times daily and atenolol 75 mg daily. She had no laboratory investigation previously until she attended a multiphasic health screening programme a year ago. Blood chemistry then apparently revealed hypokalaemia but otherwise normal results. Her serum potassium concentration was within the normal range when repeated, and no further investigation was carried out. Upon the patient's request, her serum potassium was rechecked 6 months later. This was found to be low at 3.2 mmol/L, which initiated this referral.

The patient had no significant medical history of note, and there was no family history of hypertension. Apart from her usual anti-hypertensive drugs, she was not on other medications or diuretics. She was a motivated and compliant patient, and she followed dietary salt restriction closely. She did not have history of acute muscle weakness or paralysis. On direct questioning however, she experienced increased thirst and polyuria, and the need to void a full bladder twice nightly. Physical examination was normal apart from a blood pressure reading of 154/90 mmHg. Her heart rate was regular at 60 beats/min, while on β-blockade.

Question: What is your provisional diagnosis? Comment on the significance of her history.

Answer: In a patient with hypertension and hypokalaemia, one needs to exclude mineralocorticoid hypertension due to aldosterone excess, termed primary aldosteronism. However, a thorough history is important to exclude other causes like diuretic therapy, diarrhoea, vomiting, deficient intake, renal tubular disorders, or conditions associated with intracellular potassium shift.

In subjects with hyperaldosteronism, the level of dietary salt intake exerts an important bearing on the laboratory results. This is because the renal potassium wastage mediated by hyperaldosteronism is dependent on renal tubular sodium delivery and reabsorption in the distal tubule. As the sodium-potassium exchange mechanism cannot operate fully when renal tubular sodium delivery is reduced, subjects on low dietary salt intake will show attenuated effects of hyperaldosteronism. This may explain the normal serum potassium concentration noted in this patient on the previous occasion. Even with a normal salt diet, serum potassium is found to have a sensitivity of only 75% – 80% in detecting individuals with hyperaldosteronism.

Question: What is the biochemical hallmark for mineralocorticoid hypertension? What laboratory investigations would you order for this patient?

Answer: The biochemical hallmark of hyperaldosteronism is hypokalaemic metabolic alkalosis associated with increased urinary potassium loss. Apart from hypokalaemia, we need to check if her serum and urine electrolytes fit the above biochemical picture. We will then screen for primary aldosteronism by measuring plasma aldosterone concentration (PAC) and plasma renin activity (PRA), and determine the ratio of PAC to PRA.

Question: Please comment on the following results. How does the PAC/PRA ratio help you?

Serum sodium	139 mmol/L
Serum potassium	3.3 mmol/L
Serum bicarbonate	31.8 mmol/L
Urine potassium	93 mmoL/24 hours
Urine volume	3,800 mL/24 hours
Plasma aldosterone concentration (PAC)	1,614 pmol/L (58.2 ng/dL)
Plasma renin activity (PRA)	0.07 ng/mL/h

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Answer: She has a low-normal serum potassium concentration, an inappropriately high urinary potassium excretion, and a high-normal serum bicarbonate concentration, consistent with the effect of mineralocorticoid excess. She also has a high 24-hour urine volume which is consistent with her symptoms of polydipsia and polyuria.

PAC/PRA ratio is a useful screening test for primary aldosteronism, as not all individuals with hyperaldosteronism have PAC elevated beyond the normal range. However, PAC in these subjects is inappropriately elevated in the context of suppressed PRA. A ratio of PAC (ng/dL) to PRA (ng/mL/h) greater than 20 is 95% sensitive, but only 75% specific, for primary aldosteronism. This patient has a markedly elevated PAC/PRA ratio (> 800).

It is noteworthy that false negative screening result (PAC/PRA < 20) may occur in subjects who are on low salt diet, or undergoing treatment with diuretics, angiotensin converting enzyme inhibitor, and angiotensin II receptor blocker. The test should then be repeated in a salt-repleted state, after discontinuing the drug for 2 – 4 weeks. Patients on spironolactone must discontinue the medication for 6 weeks before having PAC and PRA determinations.

Question: She underwent a salt loading test to confirm the diagnosis of primary aldosteronism. This consisted of a high dietary salt intake for three days, together with oral sodium and potassium supplements. A 24-hour urine specimen was collected on the third day. Please comment on the results:

Urine sodium	205 mmol/24 hours
Urine potassium	146 mmol/24 hours
Urine aldosterone	17.7 ug/24 hours

Answer: The diagnosis of primary aldosteronism is confirmed by demonstrating increased urinary aldosterone excretion (> 12 ug/day) despite adequate salt loading (urine sodium excretion > 200 mmol/day) and suppressed PRA (as documented earlier). With increased salt intake, we also noticed corresponding increase in her urinary potassium wastage.

Question: After confirming the diagnosis of primary aldosteronism, which of the following is your investigation of choice to localise the source of aldosterone hypersecretion: 1) CT scanning of the adrenals; 2) postural stimulation study, or 3) adrenal venous sampling?

Answer: We should first proceed to CT scanning of the adrenals using fine axial sections, as it helps to identify aldosterone producing adrenal adenoma (APA) or Conn's syndrome, an entity potentially curable by surgery. A representative scan image of our patient is shown in Fig 1, revealing a well-defined ovoid mass arising from the right adrenal gland, measuring approximately 2.3 cm in its largest dimension. The mass appears slightly hypodense to the normal adrenal glands. In the context of biochemically confirmed primary aldosteronism,

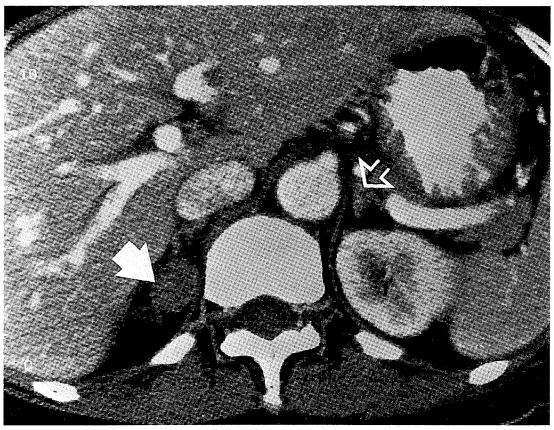

Fig 1 – CT scan (3 mm axial section) of the adrenals showing a well-defined hypodense mass arising from the right adrenal galnd (arrow), measuring approximately 2.3 cm in largest dimension. The left adrenal gland appears normal (open arrow).

the finding of a solitary well-defined adrenal macronodule (> 1 cm) in one adrenal gland and a normal-appearing contralateral gland almost unequivocally establishes the diagnosis of APA.

Question: What are the differential causes of primary aldosteronism?

Answer: Primary aldosteronism commonly arises from either APA with unilateral adrenal involvement, or bilateral adrenal hyperplasia termed idiopathic hyperaldosteronism (IHA). This differentiation is important as APA is potentially curable by unilateral adrenalectomy, whereas IHA is best managed medically. The other causes of primary aldosteronism are uncommon (Table I).

Question: Is there a need to have postural stimulation test or adrenal venous sampling in this patient prior to definitive therapy?

Answer: Both subtype differentiation studies are deemed unnecessary in this patient. The postural stimulation study is employed to differentiate between APA vs IHA. However its diagnostic accuracy at best is only 85%. Although adrenal venous sampling remains the gold standard for functional localisation or lateralisation of hyperaldosteronism, its success is highly dependent on the skill and experience of the interventional radiologist.

Question: What are the circumstances that you would consider additional testing?

Answer: Additional subtype differentiation testing is necessary if CT imaging shows normal appearing adrenals, minimal unilateral adrenal limb thickening, unilateral microadenoma (< 1 cm), or bilateral nodules. This is because small adrenal nodules are common incidental findings in hypertensive patients aged 40 – 60 years and may confuse the differential diagnosis of APA vs IHA. There are also rare causes of hyperaldosteronism with confusing findings on cross-sectional imaging, such as unilateral primary adrenal hyperplasia (PAH).

Table I – Major subtypes of primary aldosteronism

Aldosterone producing adenoma (APA) or Conn's syndrome*	50% – 65%
Bilateral idiopathic hyperaldosteronism (IHA)**	30% – 45%
Aldosteronone-producing renin-responsive adenoma (AP-RA)*	5% – 10%
Primary adrenal hyperplasia (PAH)*	5% – 10%
Aldosteorne-producing adrenocortical carcinoma*	< 1%
Glucocorticoid-remediable aldosteronism (GRA)**	< 1%

* Potentially treated by surgery.
** Potentially treated by medication.

Question: The patient heard about the postural study from another physician. In compliance with her wishes, she was admitted to the hospital for the test. After overnight recumbency, blood was taken for PAC, PRA and cortisol measurements with the patient still in bed at 0800 hours. She then got up from bed and remained in an erect posture (either standing or walking) until a repeat blood specimen was taken at 1200 hours. The following results were obtained:

Time	0800 hours	1200 hours
Posture	supine	erect
PAC	1,597 pmol/L	1,000 pmol/L
PRA	0.37 ng/mL/h	0.07 ng/mL/h
Cortisol	551 nmol/L	265 nmol/L

Comment on the postural stimulation test. How do you interpret the results?

Answer: The postural study is based on the finding that circulating aldosterone levels in patients with APA show a diurnal variation due to sensitivity to ACTH, and are relatively unaffected by changes in angiotensin II levels; whereas IHA is characterised by increased sensitivity to a small change in angiotensin II that occurs when standing. For the test to be valid, it is essential to measure the corresponding cortisol levels. In this patient, we noted a significant fall (> 30%) in PAC at 1200 hours, while the PRA remained suppressed despite the erect posture. This profile is consistent with the diagnosis of APA, in which the decline in circulating PAC occurs during the day corresponding to the fall in ACTH levels, as reflected in plasma cortisol measurements.

However, this study is not fully discriminative of the subtypes, as it has been found that some patients with APA are sensitive to angiotensin II, and that some patients with IHA are responsive to ACTH and showed diurnal variation in aldosterone secretion. Therefore, this study has a limited role in the diagnostic evaluation in centres proficient in adrenal venous sampling.

Question: Her anti-hypertensive drug was switched to spironolactone 75 mg twice daily. When reviewed 4 weeks later, she lost 2 kg and her thirst and polyuria resolved completely. Her BP was 130/84 mmHg; her serum electrolyte measurements were normal:

Serum potassium	4.5 mmol/L
Serum bicarbonate	25.2 mmol/L
Serum creatinine	74 umol/L

Comment on the use of spironolactone.

Answer: Spironolactone acts both as a specific antagonist of aldosterone and as an inhibitor of aldosterone synthesis in adenoma. In patients with primary aldosteronism, administration of spironolactone (100 – 300 mg daily for 3 – 6 weeks) is usually associated with a significant reduction in blood pressure, mild weight loss, and normalisation of serum potassium concentration. The response to spironolactone helps to define the best mode of therapy, as patients with APA who do not respond to spironolactone are not relieved of hypertension by surgical intervention.

Progress: She underwent laparoscopic right adrenalectomy. The resected right adrenal gland revealed a 2.2 cm circumscribed nodule with a characteristic bright yellow appearance (Fig 2). Histological features were compatible with adrenal cortical adenoma. Her blood pressure and serum electrolyte values were normal post-operatively, despite discontinuation of spironolactone therapy. She was well and discharged on the second post-operative day.

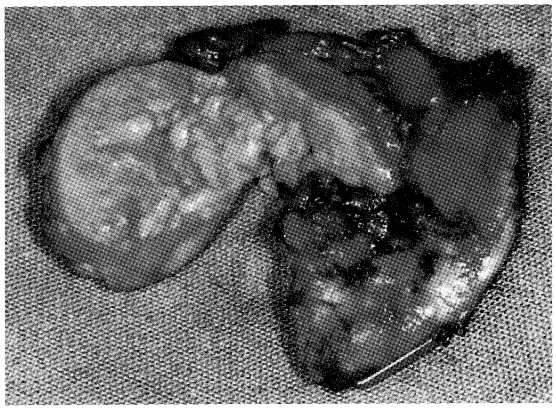

Fig 2 – The resected right adrenal gland. This reveals a circumscribed nodule with characteristic bright yellow appearance on sectioning.

DISCUSSION

Primary aldosteronism is a generic term for disorders associated with chronic aldosterone excess, which exists in a totally or partially autonomous manner in relation to the renin-angiotension system. The resulting clinical phenotype is hypertension and, in most instances, hypokalaemia. Primary aldosteronism is probably the most common form of endocrine hypertension; estimates of its incidence vary from 0.5% to 5% in the hypertensive population. The peak age distribution of this disorder is between the third and fifth decades. The most common adrenal lesion responsible for primary aldosteronism is a solitary aldosterone producing adrenocortical adenoma (APA) or Conn's syndrome. Bilateral adrenal hyperplasia or idiopathic hyperaldosteronism (IHA) accounts for the bulk of the remainder of cases. Apart from detecting primary aldosteronism, the challenge lies in correct subtype differentiation as APA is curable surgically whereas IHA is best treated medically. Glucocorticoid-remediable aldosteronism (GRA) is a rare, autosomal dominant form of hypertension in which aldosterone production comes under regulatory control of ACTH due to a fusion gene.

On clinical grounds, the hypertension of primary aldosteronism is indistinguishable from that which occurs in other disorders, as affected individuals generally do not manifest specific signs or symptoms. However, a careful history may reveal recognised features of potassium deficiency, such as nocturnal polyuria and polydipsia in our case. Other recognised symptoms include muscle weakness and decreased stamina, and acute periodic paralysis may occur in severe cases. However, the severity of hypokalaemia varies and is related in part to sodium intake. Furthermore, a substantial proportion of patients with hypokalaemia have no symptoms. It is therefore not surprising that patients with primary aldosteronism are often treated as "essential hypertension" for years until routine blood chemistry raises the suspicion of hyperaldosteronism, as illustrated by our case.

All forms of primary aldosteronism can be diagnosed biochemically by the demonstration of inappropriately raised blood aldosterone concentrations and/or urinary aldosterone excretion in the presence of suppressed plasma renin activity. When primary aldosteronism is established, the adrenal lesion must be identified and localised with the help of imaging and other subtype differentiation studies. The importance of following the appropriate evaluation steps cannot be over-emphasised, as the therapeutic approach differs markedly for different lesions. With current advances in minimally invasive surgical techniques, patients with resectable adrenal lesions need only undergo laparoscopic adrenalectomy, resulting in reduced post-operative morbidity and hospital stay.

In conclusion, this case illustrates the current approach to patients with suspected primary aldosteronism. As medicine is an evolution, the science of today may be obsolete tomorrow. Therefore, the value of many traditionally upheld endocrine tests should be re-assessed in the context of advances made in laboratory and diagnostic techniques. With the cogent need for cost-containment in medicine, it is important to recognise that most endocrine conditions can be evaluated in the ambulatory or out patient setting.

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