Hyperaldosteronism: recent concepts, diagnosis, and management

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As a cause for hypertension, aldosterone excess is now thought to be more prevalent than previously quoted in textbooks. Classical features of hypokalaemia and metabolic alkalosis can be absent even in the presence of marked hypertension. This implies the need for a high index of suspicion and possibly argues the case for routine screening, especially in patients with "difficult to treat" hypertension. Given multisystem target organ damage and increased cardiovascular risk associated with chronic uncontrolled hypertension, a readily treatable cause such as hyperaldosteronism is an important diagnosis to make. In addition, hyperaldosteronism related hypertension is now known to cover other recently identified monogenic disorders such as glucocorticoid remediable aldosteronism. These rarer monogenic hypertensive disorders provide clues to cracking the mystery behind polygenic "essential" hypertension. Apart from patients with hyperaldosteronism, a subset of the well recognised "low renin hypertension" patient group also appears to produce a dramatic and remarkable response when treated with spironolactone. We suggest that spironolactone sensitive hypertension may represent a wider spectrum of disorders where blood pressure is readily controlled by the addition of aldosterone receptor antagonist.

Aldosterone physiology

Glucocorticoids and mineralocorticoids are synthesised from cholesterol mainly in the adrenal cortex. The two forms of cytochrome *P*-450 enzymes, CYP11B1 (aldosynthase) and CYP11B2 (11 β -hydroxylase), that catalyse the final step of these synthetic pathways are encoded by two closely related genes on chromosome 8. CYP11B1 synthesises corticosterone from deoxycorticosterone in the zona fasciculata reticularis and is mainly regulated by adrenocorticotrophic hormone (ACTH). CYP11B2 catalyses the synthesis of aldosterone from deoxycorticosterone in the zona glomerulosa and its activity is principally regulated by angiotensin II and potassium; and it is weakly regulated by sodium and ACTH. As mitochondrial enzymes, CYP11B1 and 11B2 are highly sensitive to tissue oxygen concentration.

Aldosterone is the major and most potent mineralocorticoid in man. It interacts with specific intracellular receptors to form dimers which in turn bind to response elements in the promoter regions of target genes to initiate hormone mediated transcription. Precise aldosterone induced proteins have not been identified but recent evidence suggests that a member of the serine-threonine kinase pathway, serum glucocorticoid regulated kinase (sgk) regulates activity of the epithelial sodium channel (ENaC).¹ Mineralocorticoids appear to directly

modulate sgk gene transcription and furthermore, a simple hormone response element has been found in the rat sgk gene 5'-flanking region.² Sgk mRNA is rapidly stimulated by mineralocorticoids but receptor ligand activation results in both an early phase increase in ENaC activity and a late phase upregulation of ENaC number. Apart from action on ENaC in apical cells, aldosterone appears to also increase activity of the Na⁺/K⁺-ATPase pump in the basolateral membrane of distal tubular cells.³ Furthermore, rapid 2–10 min effects of aldosterone have been described that are not inhibited by mineralocorticoid receptor antagonist, spironolactone.⁴ Unknown mechanisms mediating aldosterone receptor binding, including the possibility of unknown membrane receptors not involving protein synthesis, thus remain to be defined. Nevertheless aldosterone is responsible physiologically for electrolyte balance in the kidney, salivary glands, sweat glands, and gastrointestinal tract and in the kidney it has the important function of mediating sodium retention and increasing potassium excretion.

In the renin-angiotensin-aldosterone axis, decreased renal perfusion pressure stimulates the β -adrenoreceptor dependent release of renin that is synthesised by juxtaglomerular cells. In extracellular volume overexpansion, "excessive stretch" signals in the juxtaglomerular cells result in decreased renin secretion. The substrate for renin is angiotensinogen, which is a glycoprotein of variable structure and molecular weight synthesised in the liver. Ten N-terminal amino acid residues of angiotensinogen contain the amino acid sequence of angiotensin I and angiotensin converting enzyme is responsible for the removal of two amino acids from angiotensin I to produce the key aldosterone stimulating factor, angiotensin II. Angiotensin II is itself a potent vasoconstrictor.

Clinical features and making the diagnosis

Conn's original description was that of a patient with hypertension, hypokalaemia, and neuromuscular symptoms associated with an aldosterone-producing adrenal adenoma.⁵ It is now recognised that the same clinical and biochemical picture can be produced by other conditions in which there is aldosterone excess without adenoma. Primary aldosteronism either through adrenal adenoma or adrenal hyperplasia is characterised by low or undetectable plasma renin activity suppressed via negative feedback by autonomous aldosterone secretion. While in some instances, the plasma aldosterone level is high as would be expected; it can also be within the normal range. Instead the aldosterone:renin ratio (ARR) appears to be a more reliable means (93% sensitivity⁶) of identifying patients with

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primary hyperaldosteronism and whose hypertension is treatable by the aldosterone receptor antagonist, spironolactone.

The first study using the ARR was published in 1981 where out of 348 hypertensive patients who were screened, nine were found to have adrenal adenoma using a much higher cut off ARR of 2081 units together with subsequent nuclear scintigram and computed tomogram.⁷ In this study, only three of the nine had potassium less than 3.5 mmol/l. Plasma aldosterone levels were equally non-discriminatory. All nine had suppressed plasma renin activity but so did 39% of all the other 348 patients without adenomata. If present day ARR cut off of 750 units were used, more patients may have been diagnosed as having primary aldosteronism. In the late 1990s Gordon showed that by screening all hypertensive patients reviewed in a tertiary centre for ARR >750 units, the prevalence of primary aldosteronism was closer to 15% than the 1% that has previously been quoted in textbooks.⁸ Percentages of prevalence based on the finding of a raised ARR have ranged from 2.7% to 32%.⁹

In a primary care setting, a group in Dundee has recently shown that the prevalence of primary aldosteronism diagnosed through a high ARR was 25%.¹⁰

In an Australian tertiary practice, Hamlet *et al* reportedly found the recognition of hyperaldosteronism as defined by a high ARR abruptly increased from two to five cases per year before routine use of the ARR, to over 50 per year after its use.¹¹ In their screening programme, Hamlet *et al* also found that the majority of patients (70%) with primary aldosteronism were normokalaemic. Patients can rarely present with severe resistant hypokalaemia with symptoms of muscle weakness and paraesthesia. We have observed that hypokalaemia is more likely to occur after starting thiazide diuretic as an antihypertensive. But hypokalaemia is clearly not necessary for the diagnosis of hyperaldosteronism. In fact, patients with primary aldosteronism are more likely to be normokalaemic. In our practice we have noted that patients with primary aldosteronism almost always have serum sodium above 140 mmol/l.

Under normal circumstances, aldosterone levels, initially measured decubitus in the early morning hours, increase and double after four hours of erect posture. This was previously used to differentiate between adrenal adenoma (tumour) and idiopathic zona glomerulosa hyperplasia because in hyperplasia marked enhancement of adrenal responsiveness to angiotensin II resulted in higher aldosterone levels in the erect posture. In patients with adenoma on the other hand, it was observed that the tumour responded more to ACTH instead of angiotensin II. In these patients therefore, aldosterone levels were unchanged with erect posture and they followed a circadian rhythm similar to that for cortisol.

However the monogenic disorder of glucocorticoid remediable aldosteronism or familial hyperaldosteronism I was discovered where there is adrenocortical hyperplasia with no apparent progression to adenoma formation

and aldosterone synthesis is angiotensin II insensitive but ACTH sensitive. In contrast, familial hyperaldosteronism II is yet another condition that has been described where patients have cortical hyperplasia,¹² and in many kindreds there is an associated progression to adenoma (tumour) formation where aldosterone synthesis is not glucocorticoid remediable and remains angiotensin II sensitive. Familial hyperaldosteronism II has recently been mapped to chromosome 7p22.

On the background of this, difference in aldosterone levels with change of posture therefore requires careful interpretation in relation to family history and adrenal imaging results. When entire adrenal glands were removed in cases of a solitary benign adenoma, the "non-tumorous" section of zona glomerulosa often appeared histologically hyperplastic, consisting of multiple small cortical nodules. This may well represent a spectrum of overlap as seen in familial multiple neoplasia syndromes where both neoplasia and hyperplasia are variously and sometimes simultaneously expressed. The genetic abnormality is unlikely to be limited to cells within the adenoma.

When determining the ARR, concomitant antihypertensive therapy can alter renin and aldosterone levels. Calcium channel antagonists suppress aldosterone synthesis. Angiotensin converting enzyme inhibitors suppress aldosterone levels as would the newer angiotensin II receptor antagonists. Thiazide diuretics lead to increase in renin levels more marked than that of aldosterone. All antihypertensives in these classes, however, improve the discriminatory power of the ARR. A false negative is unlikely in view of the autonomous nature of aldosterone excess. However β -blockers suppress renin synthesis and may lead to a false positive and we generally require patients to stop β -blocker therapy one week before testing for plasma renin activity and aldosterone in our protocols. Others believe valid data can be obtained even in the presence of various drugs.¹³

We have previously used a protocol of daily salt loading with 10 g sodium two weeks before testing for plasma renin activity and aldosterone. The rationale behind this is to suppress plasma aldosterone, which will be seen in normal subjects but not in patients with primary aldosteronism. In our experience this protocol has not proved to increase the diagnostic power of the ARR significantly to justify the complex and uncomfortable testing method. Measurement of 24 hour urinary sodium excretion may be an easier alternative to give an idea of sodium intake. Others have also employed suppression tests using the synthetic mineralocorticoid, fludrocortisone. Although useful for clinical study purposes we have generally found suppression tests in hyperaldosteronism lacking in diagnostic value.

Management

ALDOSTERONE EXCESS—ADRENAL ADENOMA OR HYPERPLASIA

Once the diagnosis of aldosterone excess is made with a high ARR, the next investigational steps are radiological.

The tool of choice for imaging adrenal glands requires superior resolution and we have generally preferred using magnetic resonance imaging unless there are technical contraindications. The diagnosis of adrenal adenomata is likely if discrete nodule or nodules are detected. Unilateral disease suggests that surgical resolution of hypertension is possible. Further to magnetic resonance imaging, differential adrenal vein sampling is the logical next step to confirm or refute unilateral disease and help predict the success of unilateral adrenalectomy. Adrenal vein catheterisation is technically difficult to perform but is a useful tool in the hands of a skilled operator. Part of the difficulty lies with catheterising the right adrenal vein which unlike the left drains, in the normal human anatomy, into the right renal vein instead of directly into the inferior vena cava. Apart from the left and right adrenal veins, blood is taken from the suprarenal inferior vena cava. Aldosterone and cortisol concentrations are determined from the collected blood samples. The reason for determining cortisol concentration is twofold. The aldosterone:cortisol ratio helps to provide a normalised ratio for bilateral comparison. If a unilateral adrenal gland were responsible for excess aldosterone production, one would expect the ratio to be at least thrice that of the contralateral side. On the contralateral side, aldosterone secretion is expected to be suppressed. The ratio on the suppressed contralateral side should approximate that seen in the suprarenal inferior vena cava. The caveat to looking at the aldosterone:cortisol ratio is one needs to be certain that cortisol concentrations are comparable bilaterally because occasionally the right adrenal vein may receive tributaries from the hepatic circulation and give rise to much higher cortisol levels on that side. The second purpose of determining cortisol concentration is to confirm that the catheters are within the adrenal veins at the time of blood sampling. Cortisol concentrations in the adrenal veins should approach twice of that found in the suprarenal inferior vena cava sample.

Nuclear scintigraphy with ^{131}I -labelled iodomethyl-19-norcholesterol or ^{75}Se -6-selenomethylcholesterol is another possible method for distinguishing unilateral disease from bilateral hyperplasia but generally scintigrams are difficult to interpret in patients taking various antihypertensive medications. Spironolactone must be stopped for at least six weeks before scanning.

In patients who have homogenous or nodular hyperplasia or normal looking adrenal glands radiologically, surgery is inappropriate and sometimes not curative. Antihypertensive treatment with the inclusion of spironolactone is usually adequate for blood pressure control. Often, response to the addition of spironolactone is dramatic and many patients can be maintained adequately on spironolactone monotherapy. After an initial high dose therapy it may be possible to reduce to a maintenance dose of 25 to 50 mg/day. The side effects of impotence, gynaecomastia, and menorrhagia are sometimes intolerable and unacceptable; such patients may be given amiloride as an

alternative (amiloride acts directly on ENaC to reduce sodium retention). Patients with angiotensin II sensitive adenoma or hyperplasia may need further blood pressure control with angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists.

ALDOSTERONE EXCESS—OTHER CAUSES

Glucocorticoid remediable aldosteronism (familial hyperaldosteronism I) is the first monogenic disorder related to hypertension that has been identified.¹⁴ In this autosomal dominant disorder there is a single crossover mutation where aldosterone synthesis becomes under the control of ACTH. The aldosterone synthase (CYP11B2) and 11β -hydroxylase (CYP11B1) genes which both lie on chromosome 8q21-q22 undergo mutation possibly during meiosis to form a hybrid gene that is ACTH sensitive (like CYP11B1) but has the coding sequence of CYP11B2 (aldosterone synthase). In this condition, there is adrenocortical hyperplasia which may be nodular, and histological features suggest overactivity of the zona fasciculata. There is no report of progression to tumour formation. Patients with this condition tend to be young hypertensives who are otherwise asymptomatic, and diagnosis can be made by dexamethasone suppression of plasma aldosterone or by simple Southern blotting now with the discovery of the genetic defect. Treatment in this condition is glucocorticoid therapy with low dose dexamethasone to suppress ACTH production, which in turn suppresses aldosterone synthesis.

APPARENT ALDOSTERONE EXCESS

Some patients have hypertension with features of hyperaldosteronism (hypokalaemia, decreased renin activity) but actually have low or undetectable aldosterone. Such conditions include rare congenital conditions such as apparent mineralocorticoid excess, Liddle's syndrome, and recently identified activating "gain of function" mutations in the mineralocorticoid receptor.¹⁵ Liquorice intoxication produces a similar syndrome to apparent mineralocorticoid excess.

In the congenital condition of apparent mineralocorticoid excess there is a genetic absence of the cell specific enzyme, 11β hydroxysteroid dehydrogenase isoform 2 ($11\beta\text{HSD}2$). $11\beta\text{HSD}2$ converts cortisol to inactive cortisone in distal tubular cells. Under normal circumstances cortisol exists in 100-fold higher circulating concentrations than aldosterone and has a high affinity for the mineralocorticoid receptor. In distal tubular cells therefore, $11\beta\text{HSD}2$ is responsible for converting and inactivating glucocorticoids so that the mineralocorticoid receptors in these cells are only activated by mineralocorticoids and protected from the local effects of glucocorticoids. In apparent mineralocorticoid excess where there is $11\beta\text{HSD}2$ deficiency, cortisol is unconverted and free to bind with high affinity to mineralocorticoid receptor thereby activating it. Plasma renin activity and plasma aldosterone are both markedly suppressed with a raised ratio of urinary cortisol to cortisone metabolites. Children with congenital apparent mineralocorticoid

excess invariably have severe hypertension, and high morbidity and mortality. Spironolactone may control electrolyte imbalance but blood pressure control usually requires further agents such as angiotensin converting enzyme inhibitors and thiazide diuretics. Low dose dexamethasone (dexamethasone does not bind mineralocorticoid receptor) may be of major benefit by suppressing endogenous cortisol production and removing the mineralocorticoid receptor agonist. The gene for 11 β HSD2 is found on chromosome 16q22 and so far 11 mutations have been identified. Analysis of kindreds with this enzyme defect has shown an autosomal recessive inheritance.

The acquired form of apparent mineralocorticoid excess is seen with excess ingestion of liquorice or related drugs such as carbenoxolone. Liquorice contains an active component glycyrrhetic acid and carbenoxolone is a hemisuccinate derivative of this. Glycyrrhetic acid binds to and potentially inhibits 11 β HSD, preventing the renal conversion of cortisol to cortisone. The clinical picture mimics a milder form of congenital apparent mineralocorticoid excess. Plasma renin activity and plasma aldosterone are suppressed but the ratio of urinary cortisol to cortisone metabolites is less markedly raised.

Liddle's syndrome is the condition where "gain-of-function" mutations are found in the subunits of the epithelial sodium channel such that there is sodium retention and potassium loss, mimicking hyperaldosteronism. In these patients, however, aldosterone and renin levels, as in apparent mineralocorticoid excess, are extremely suppressed. Treatment, however, is similar to Conn's syndrome and involves spironolactone but often also requires amiloride or triamterene.

Spironolone sensitive hypertension: does this represent a spectrum of diseases?

Spironolactone can be used to control hypertension in patients with adrenal adenomata and hyperplasia. Other indications are rarer genetic conditions aforementioned. In identifying hypertensive patients who may be treatable with spironolactone, a high ARR is the useful discriminant regardless of imaging findings. However, we are accumulating evidence (M J Brown *et al* 2001, unpublished data) that show patients with low suppressed plasma renin activity, normal aldosterone level, and *normal* or acceptable ARR appear to have hypertension equally responsive to spironolactone. The following three cases of longstanding hypertension illustrate the suggestion that spironolactone sensitivity may represent a spectrum not previously thoroughly appreciated.

Case reports

CASE 1

A man, aged 64, had a 10 year history of hypertension that was "difficult to treat" in spite of attempts with angiotensin converting enzyme inhibitors, calcium channels blockers, β -blockers and diuretics, singly and in combination. He was seen in our clinic with a blood pressure of 170/100 mm Hg, on atenolol 100 mg

and lisinopril 20 mg twice a day. Interestingly, a year before he had had the dramatic experience of an out-of-hospital cardiac arrest and further subsequent episodes of ventricular tachycardia, all of which eventually led onto electrophysiological studies and the implantation of an automated cardiac defibrillator. Routine tests revealed a persistently low potassium of 3.2 mmol/l; and aldosterone and renin profiling led to the finding of a high ARR (4250 units). Computed tomography revealed a 1 cm nodule in the left adrenal gland and he is presently waiting to undergo differential adrenal vein sampling. Figure 1A shows his dramatic blood pressure response upon the addition of spironolactone.

CASE 2

A 68 year old woman had high blood pressure for 40 years and despite being on atenolol 100 mg, enalapril 20 mg, bendrofluazide 2.5 mg, indoramin 12.5 mg, lacidipine 60 mg, hydralazine 50 mg twice a day and clonidine 75 μ g twice a day, her blood pressure was 230/110 mm Hg. Her electrolytes showed borderline hypokalaemia (3.5 mmol/l); plasma aldosterone was within normal limits (290 pmol/l) but plasma renin activity was markedly suppressed (<0.2 pmol/ml/hour). The ARR was high at 1450 units. Magnetic resonance imaging

Figure 1 Blood pressure response on taking spironolactone in (A) case 1, (B) case 2, and (C) case 3.

showed normal looking adrenal glands. Figure 1B shows her dramatic blood pressure response upon the addition of spironolactone.

CASE 3

A man, aged 57, had a six year history of uncontrolled hypertension and blood pressure remained high at 220/116 mm Hg in spite of bisoprolol 5 mg and losartan 100 mg. Plasma electrolytes were normal, plasma aldosterone was normal (190 pmol/l) but plasma renin activity was low (0.4 pmol/ml/hour). The ARR was acceptable at 600 units and computed tomography showed normal looking adrenal glands. Figure 1C shows his blood pressure response upon the addition of spironolactone.

Case 1 represents the classical spironolactone response of patients with hyperaldosteronism and adrenal adenomata. Persistent hypokalaemia may well be the explanation in part for his ventricular tachyarrhythmias. Surgery is an option if proof of unilateral disease and contralateral suppression is found.

Case 2 illustrates the practical usefulness of a high ARR in that hypertension may be treatable with spironolactone despite normal looking adrenal glands on radiological imaging. Lim *et al* have previously described a similar cohort of patients with spironolactone sensitive hypertension.¹⁰ In these patients, adrenal micronodules cannot be excluded but differential adrenal venous sampling as a prelude to surgical therapy is difficult to justify given the normal scan findings. Alternatively, the longstanding history of hypertension, as seen with this patient, implies mechanisms of inappropriate aldosterone secretion devoid of adenomata or hyperplasia formation.

Case 3 represents a group of patients with spironolactone sensitive hypertension not previously described. These are patients who, as case 2, have normal aldosterone level, low suppressed renin activity, normal adrenal glands on imaging but, unlike case 2, have a "normal" ARR. We are accumulating data on more than 20 of such patients in our tertiary practice and primary care screening (M J Brown *et al* 2001, unpublished data), all of whom have had the dramatic response to spironolactone as seen in fig 1C. We now call this group normoaldosterone spironolactone sensitive hypertension (NASSH). The low suppressed renin activity appear to represent a further overlap with the well recognised subset of essential hypertension known as "low renin essential hypertension" (LREH). Classically, patients with LREH are salt sensitive and are more likely to respond to diuretics than to agents that block the renin system. In NASSH, however, we have found that thiazide diuretics are ineffective and often unmask hypokalaemia. Recent evidence has refuted previous belief that patients with LREH maintain normal basal plasma aldosterone levels in the face of suppressed renin system via excessive responsiveness to angiotensin II.¹⁶ Instead when stimulated with a low sodium diet, LREH patients demonstrated only a small rise in aldosterone and blunted responsiveness to angiotensin II infusion. This

observation has practical value in understanding the physiology underlying NASSH. In one study, a subset of patients with a normal/high level of renin activity demonstrated a similarly flat adrenal response to angiotensin II infusion when stressed by salt restriction.¹⁶ This subset of normal/high renin hypertensives appears to be a distinct group of essential hypertensives known as non-modulators. Although adrenal responsiveness to angiotensin II is lacking in LREH patients, angiotensin II infusion produces a pressor response that is significantly greater compared with that seen in non-modulating essential hypertension, modulators, and normotensive controls. It has been shown repeatedly in hypertension marked by sodium retention that there is a heightened sensitivity of the vasculature to angiotensin II attributed to upregulation of vascular angiotensin II receptors. The overlap between LREH and NASSH is further suggested by the additive blood pressure response in NASSH patients to the combination therapy of spironolactone and an angiotensin II receptor antagonist such as irbesartan. The pathophysiological mechanisms underlying NASSH remain to be determined. Meanwhile using spironolactone to treat NASSH patients, who usually have a longstanding history of resistant hypertension, produces dramatic and remarkably impressive results.

Conclusion

Recent evidence suggests that the prevalence of primary hyperaldosteronism is higher than originally thought. Even in the absence of hypokalaemia and especially in patients with difficult to control hypertension, ARR may be useful. Difficult to control hypertensives are ones who do not respond in spite of three or more antihypertensive drugs.⁹ In patients who have a high ARR, treatment with spironolactone has been shown to readily produce successful blood pressure control. Surgical therapy for Conn's adenoma may be considered after appropriate radiological imaging and adrenal venous sampling.

While low renin essential hypertensives with a normal ARR are classically treatable with thiazide diuretics, there appears to be a subset of patients who are treatable instead with spironolactone but not thiazides. We have called this subset "normoaldosterone spironolactone sensitive hypertension" or NASSH. We propose that spironolactone sensitive hypertension may represent a wider spectrum of conditions potentially treatable by the simple addition of a single tablet. This may raise the justification for a trial of spironolactone in patients with resistant hypertension, especially in situations where there is inadequate access to plasma aldosterone or renin measurement. Other patients with the clinical and biochemical picture of hyperaldosteronism may alternatively have rarely causes of hypertension including glucocorticoid remediable aldosteronism, Liddle's syndrome, and acquired apparent mineralocorticoid excess.

A summary of conditions described is shown in table 1.

Table 1 Summary of conditions described in the text

	Key pathological features
Conn's adenoma	<ul style="list-style-type: none"> ● High aldosterone:renin ratio (ARR) ● Adenoma on adrenal imaging ● Adrenal vein sampling and subsequent surgery may be considered if there is unilateral disease and contralateral suppression of aldosterone secretion ● However hypertension usually responds well to spironolactone
Adrenal hyperplasia	<ul style="list-style-type: none"> ● Usually bilateral disease ● High ARR ● Bulky adrenal glands on imaging ● Hypertension control usually achieved with spironolactone
Glucocorticoid remediable aldosteronism or familial hyperaldosteronism I	<ul style="list-style-type: none"> ● First monogenic disorder in hypertension to be described ● Adrenocortical hyperplasia without progression to adenoma formation ● Aldosterone synthesis is adrenocorticotrophic hormone (ACTH) sensitive ● Young hypertensives, otherwise asymptomatic ● Diagnosis made by dexamethasone suppression of plasma aldosterone or simple Southern blotting ● Blood pressure control achieved by low dose dexamethasone therapy to suppress ACTH
Familial hyperaldosteronism II	<ul style="list-style-type: none"> ● Adrenocortical hyperplasia with associated adenoma formation ● Aldosterone synthesis is not ACTH sensitive but angiotensin II sensitive
Apparent mineralocorticoid excess	<ul style="list-style-type: none"> ● Features of hyperaldosteronism (hypokalaemia and decreased renin activity) ● But low/undetectable aldosterone ● Genetic absence (likely autosomal recessive) of 11β-hydroxysteroid dehydrogenase 2, which is responsible for cortisol inactivation in distal tubular cells ● Un-inactivated glucocorticoids therefore act on mineralocorticoid receptors with high affinity to produce deleterious effects ● Congenital apparent mineralocorticoid excess has high morbidity and mortality ● Management usually requires spironolactone and other antihypertensive agents, together with low dose dexamethasone for suppressing endogenous cortisol synthesis
Acquired apparent mineralocorticoid excess	<ul style="list-style-type: none"> ● Ingestion of liquorice or related drugs such as carbenoxolone, which binds to and inhibits 11β-hydroxysteroid dehydrogenase 2
Liddle's syndrome	<ul style="list-style-type: none"> ● "Gain-of-function" mutations found in the subunits of the epithelial sodium channel, resulting in sodium retention and potassium loss ● Renin and aldosterone levels, as in apparent mineralocorticoid excess, are markedly suppressed ● Blood pressure control requires spironolactone, and often amiloride
Normoaldosterone spironolactone sensitive hypertension (NASSH)	<ul style="list-style-type: none"> ● As defined by Brown <i>et al</i> (see text), likely to be a subgroup of low renin hypertension ● Suppressed renin activity ● Normal plasma aldosterone and normal ARR ● Normal adrenal glands on imaging ● Marked blood pressure response to spironolactone, usually on the background of longstanding, difficult to treat hypertension

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Learning points

- Hyperaldosteronism, as a cause of hypertension and as defined by high aldosterone:renin ratio (ARR), has a higher prevalence (~10%) than previously appreciated.
- Ethnic subgroups have classically been shown to have predominantly low renin activity if hypertensive. The high prevalence of hyperaldosteronism however appears to be found even in the primary care setting in Scotland and in mixed population studies in Australia.
- Measuring plasma aldosterone concentration and plasma renin activity is useful, and hypertensive patients with high ARR are likely to respond to spironolactone.
- If surgery is to be considered, the investigation of choice in patients with Conn's syndrome who have scan evidence of adrenal adenoma, is differential adrenal vein sampling.
- Even in the absence of adrenal gland abnormality on scan, patients with high ARR are responsive to spironolactone.
- We have identified patients (M J Brown *et al*, unpublished results) with low plasma renin activity and normal ARR but show dramatic response to spironolactone and chosen to name this normoaldosterone spironolactone sensitive hypertension (NASSH.)
- We suggest that there is a spectrum of spironolactone sensitive hypertensive patients, overlapping further with patients conventionally called low renin hypertensives who have traditionally shown best response to thiazide diuretics.
- As with other causes of hyperaldosteronism where genetic mutations have been identified, genetic variation in these spironolactone sensitive patients remains to be elucidated.

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