Hyperaldosteronism can be defined as excessive levels of aldosterone which may be independent of the renin-angiotensin axis (primary hyperaldosteronism) or due to high renin levels (secondary hyperaldosteronism).

Epidemiology

Many decades ago the prevalence of primary aldosteronism as a cause of hypertension was thought to be very low - figures like 0.5%-2% had been quoted. However, it has subsequently emerged that these low prevalence rates were simply because the condition was not being looked for. Primary aldosteronism is now considered to be the most common and curable form of secondary hypertension.

Following this there began a spate of almost routine investigation looking for hyperaldosteronism in patients with hypertension (regardless of potassium levels). This led to higher estimated rates of prevalence in the order of 5%-10%. This too has been disputed and it is most likely that primary hyperaldosteronism is prevalent in patients with resistant hypertension, but levels are lower in the general unselected hypertensive patients (more in the order of 0.1%-4%).

Aetiology

Excessive aldosterone levels act at the distal renal tubule, promoting sodium retention, which results in water retention and volume expansion with hypertension. There is also excretion of potassium, resulting in hypokalaemia.

Causes

Primary hyperaldosteronism

Adrenal adenoma

- This is known as Conn's syndrome. It was first described in 1956 by Dr Jerome Conn, an American endocrinologist, who discovered an aldosterone-secreting adenoma in a 34-year-old patient who had a long history of periodic cramps associated with occasional complete lower limb paralysis.
- Adrenal adenoma accounts for more than 80% of all cases of hyperaldosteronism.
- Adenomas are usually unilateral and solitary.

Adrenal hyperplasia

- In bilateral adrenal hyperplasia (BAH) the adrenal cells become hyperplastic, resulting in excessive secretion of aldosterone. This accounts for 15% of all cases of hyperaldosteronism.
- There is also a much rarer recognised entity of unilateral adrenal hyperplasia, which is treated by adrenalectomy.

Familial hyperaldosteronism

- This was first described when it was noted by Sutherland in 1966 that a father and son both had hypertension, low plasma renin activity and increased aldosterone which responded to steroids. There are two forms: type 1 is glucocorticoid-remediable aldosteronism (GRA) and type 2 is characterised by inherited aldosterone-producing adenoma or inherited BAH.
- In GRA the regulatory portion of the 11b-OH gene binds to the aldosterone synthase gene; thus, adrenocorticotropic hormone (ACTH) release leads to stimulation of this abnormal chimera and excessive aldosterone production. This aldosterone is produced from the zona fasciculata rather than the usual site of aldosterone production - the zona glomerulosa. The pattern of inheritance of GRA is autosomal dominant.
- GRA is associated with hypertension that begins at an early age, usually in the twenties, and it can be resistant to treatment. Patients with GRA can develop haemorrhagic strokes and are usually screened for cerebral aneurysms on a regular basis. This subset of patients is usually normokalaemic until started on diuretics, when they become profoundly hypokalaemic.

Adrenal carcinoma

- This is a rare cause of primary hyperaldosteronism but one that should not be missed.
- It is usually only diagnosed once an adrenal adenoma has been removed and examined histopathologically.

Presentation

Classic features include:
Hypertension.
Hypokalaemia (usually <3.5 mmol/L, although 70% of patients may be normokalaemic).
Metabolic alkalosis.
Sodium may be normal or at the high end of normal.

The presence of hypokalaemia and alkalosis appears to be not as common as once thought; therefore, a high index of suspicion is needed.

- Patients may also have polyuria and subsequent polydipsia due to reduced ability of the kidneys to concentrate urine.
- Weakness may be present from hypokalaemia.
- Headaches and lethargy may also be present.

**Case finding - looking for primary hyperaldosteronism**
- Establish whether the patient’s blood pressure is under control and whether the treatment of their blood pressure been difficult.
- Request U&E - establish whether hypokalaemia is present. If so, consider primary hyperaldosteronism. Even if U&E testing is normal, primary hyperaldosteronism may be present (especially if blood pressure is resistant to therapy).
- If primary hyperaldosteronism is possible, consider requesting renin activity - if it is normal or high, this virtually excludes primary hyperaldosteronism.
- If renin activity is low, request aldosterone levels and referral to specialists.
- If renin activity is high and high blood pressure is present, consider investigating for renovascular causes of hypertension and coarctation if appropriate. Again refer to specialists for further management.

**Investigations**
Testing renal function and renin activity and aldosterone levels should be performed whilst the patient has been off diuretics for at least four weeks and off beta-blockers and dihydropyridine calcium-channel blockers for at least two weeks. Patients should also stop steroids, potassium supplements and laxatives.

- **U&Es** - may show hypokalaemia and hypernatraemia.
- **Spot renin and aldosterone levels** - aldosterone levels are raised and renin should be low (if renin is high or normal it virtually excludes the diagnosis of primary hyperaldosteronism).
- **ECG** - may show arrhythmias from electrolyte imbalance.
- **CT/MRI scans**:
  - These methods can be used to locate an adrenal adenoma and may also pick up hyperplasia. CT scanning has a lower specificity compared with MRI scanning but is still the first-line initial imaging mode.
  - Other imaging techniques can be used - eg, CT contrast washout analysis, single-photon emission computed tomography (SPECT) or positron emission tomography (PET)/CT.

- **Selective adrenal venous sampling** - is the gold standard for localising the cause of primary hyperaldosteronism.[10]
- **Genetic testing** - is available for GRA.

**Lying and standing aldosterone/renin levels**
- Aldosterone is affected by upright posture and therefore samples are taken lying down and then repeated after being upright for a few hours.
- It is a good idea to check with your local centre, as some will still perform salt loading and lying/standing renin/aldosterone levels.
- In general, in primary hyperaldosteronism due to hyperplasia, the plasma aldosterone increases after four hours of standing, usually by more than 30%. On the other hand, there is usually no alteration in renin/aldosterone levels with posture in the presence of an adrenal adenoma.[11]
- These are only guidelines and thus lying/standing levels need to be interpreted with caution, taking into account the patient's history and the results of imaging investigations.[11]

**Salt loading and aldosterone/renin levels**
- The salt loading test can be used for further confirmation of primary aldosteronism - although it is also being used less.[11]
- The patient is loaded with salt (high-sodium diet and slow-release sodium tablets) for two weeks before samples are taken. The salt should suppress plasma aldosterone. Aldosterone/renin, cortisol and bicarbonate levels are measured.
- Failure to suppress aldosterone confirms primary hyperaldosteronism.[11]
- In the past, fludrocortisone has been used to suppress aldosterone, rather than salt; this is probably only useful in research settings.
- Salt loading is being used less and less as it does not enhance the diagnosis rate and is time-consuming.[11]

**Interpreting renin/aldosterone results**
- The aldosterone/renin ratio can be used as a screening test for primary hyperaldosteronism.
- Patients with hypertension and hypokalaemia or resistant hypertension should be screened.
If the ratio is >800 then patients should be investigated with further imaging to locate the source. Some specialist centres may also use isolated aldosterone levels to improve specificity (if aldosterone is >1,000 with a raised aldosterone/renin ratio there is almost 90% specificity). The sensitivity is between 75%-100% and specificity is also similar. In Afro-Caribbean patients the ratio combined with the absolute aldosterone level is a better screening tool, as this group of patients tends to have a low renin.

However, antihypertensive medication can adversely affect results of the aldosterone/renin ratio - eg, false positives occur with beta-blockers and false negatives occur with diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists (AIIRAs) and dihydropyridine calcium-channel blockers. Alpha-blockers do not appear to have an effect on the aldosterone/renin ratio.

Differential diagnosis of hyperaldosteronism

<table>
<thead>
<tr>
<th>Differential diagnosis of hyperaldosteronism with low renin</th>
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<tbody>
<tr>
<td>Primary hyperaldosteronism (adenoma, BAH, GRA, carcinoma).</td>
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<tr>
<td>Congenital adrenal hyperplasia.</td>
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<table>
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<tr>
<th>Differential diagnosis of hyperaldosteronism with high renin</th>
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<tbody>
<tr>
<td>Renal artery stenosis (RAS).</td>
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<tr>
<td>Coarctation of the aorta.</td>
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<td>Fibromuscular dysplasia.</td>
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<td>Renin-secreting tumours.</td>
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<td>Diuretic use.</td>
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The main diagnosis to consider is RAS, in which patients will also have hypertension and hypokalaemia. If RAS is suspected then consider the following investigations:[14]

- U&E - hypokalaemia and renal impairment may be present.
- Ultrasonography of the renal tract - may show asymmetrically sized kidneys or small kidneys.
- Mercaptoacetyltriglycine (MAG3) or dimercaptosuccinic acid (DMSA) scans - these tests provide information about the relative function of each kidney and its blood supply. They can also give information about kidney size and obstruction.
- Renal arteriogram is the gold standard and will allow angioplasty to take place if indicated.
- Renin and aldosterone levels will be high.

Cushing's disease may also present with hypertension and hypokalaemia but both the aldosterone and renin levels are low.

Treatment

**Conn's syndrome**

Medical management is used in the period prior to surgery - which is the definitive treatment. Medical management involves the use of aldosterone antagonists - eg, spironolactone.[15]

Surgical treatment involves adrenalectomy. Laparoscopic surgery is safe and effective and may be better than open surgery.[16, 17] However, hypertension may persist after removal of the adenoma, due to effects of the previous hypertension on vasculature.

More recently, the use of CT-guided acetic acid injections into small functioning adenomas is proving promising.[18] However, the data at present are only from very small numbers of patients.

**BAH**

The treatment is medical with aldosterone antagonists:

- Amiloride is a potassium-sparing diuretic which may be useful, as it counteracts hypokalaemia; however, it lacks mineralocorticoid inhibition and is only a weak antihypertensive agent. This makes the use of amiloride less attractive.[19]
- Spironolactone is a nonselective aldosterone antagonist and thus blocks not only aldosterone receptors but also testosterone receptors, leading to side-effects such as gynaecomastia, menstrual problems and erectile dysfunction.
- Eplerenone is a relatively new selective aldosterone antagonist and therefore does not have the same troublesome side-effects as spironolactone. The role of eplerenone in the treatment of primary hyperaldosteronism has not been clearly evaluated.

**GRA**
This is usually responsive to steroids and dexamethasone is used initially for four weeks. The steroids act back on ACTH switching off the drive to aldosterone production. However, if the patient continues to be hypertensive then the patient should be started on spironolactone.
Secondary hyperaldosteronism

This is the result of excessive renin in the circulation, which stimulates normal adrenals to produce aldosterone.

Causes

These include:

- Diuretics
- Congestive cardiac failure
- Hepatic failure
- Nephrotic syndrome
- RAS
- Malignant hypertension

Investigations and treatment should be directed towards the underlying cause.

Prognosis

Prognosis is good in treated patients with primary hyperaldosteronism. However, patients may continue to be hypertensive and require lifelong antihypertensive therapy. Risk factors for long-term hypertension include older age at diagnosis.

An excessive aldosterone level has a harmful effect on cardiac function by resulting in myocardial fibrosis and this can be offset by use of aldosterone antagonists.

The Randomized Aldactone Evaluation Study (RALES) showed that spironolactone markedly reduced mortality in patients with congestive cardiac failure. It may be that spironolactone also benefits cardiac function in primary hyperaldosteronism.

Further reading & references


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