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Editor-in-Chief

Frank J. Domino, MD
Professor and Director of Predoctoral Education
Department of Family Medicine and Community Health
University of Massachusetts Medical School
Worcester, Massachusetts

Associate Editors

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Professor and Senior Vice-Chairman
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Worcester, Massachusetts

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5MinuteConsult

ALDOSTERONISM, PRIMARY

Vicente T. San Martin, MD • Rodolfo J. Galindo, MD

BASICS

DESCRIPTION

- Clinical syndrome of excess aldosterone production, independent of renin secretion, and nonsuppressible by sodium (Na^+) loading.
- Classically manifested by hypertension (HTN) and hypokalemia (about half of the patients are normokalemic).
- Systems affected: cardiovascular, endocrine, renal
- Synonym(s): hyperaldosteronism, Conn syndrome

EPIDEMIOLOGY

- Since the initial case by Dr. Jerome Conn in 1954, the epidemiology has changed significantly.
- Previously considered a rare cause of HTN.
- Currently considered the most common cause of secondary HTN.

Prevalence

- Affects 5–10% of patients with HTN.
- Up to 10–30% in certain groups: moderate/severe HTN, resistant HTN, HTN plus hypokalemia, HTN plus adrenal incidentaloma, HTN plus sleep apnea.
- Commonly diagnosed in the 3rd to 5th decade of life.

ETIOLOGY AND PATHOPHYSIOLOGY

- Bilateral idiopathic hyperplasia (BIH): 60%.
- Aldosterone-producing adenoma (APA): 30–40%.
- Unilateral adrenal hyperplasia, adrenocortical carcinoma (ACC), and familial hyperaldosteronism (FH): rare <1%.
- Aldosterone excess results in:
  - Renin suppression via feedback mechanism.
  - HTN due to volume expansion and Na^+ retention.
  - Low potassium (K+) due to increased renal losses.
  - Metabolic alkalosis due to renal hydrogen losses.

Genetics

- FH syndromes
  - Type I: autosomal dominant, ACTH-induced aldosterone secretion, glucocorticoid-remediable aldosteronism (GRA).
  - Type II: autosomal dominant, familial APA or BIH type, not suppressible by glucocorticoids.
  - Type III: germline mutation in the K+ channel gene KCNJ5, increased aldosterone production, not suppressible by glucocorticoids; concurrence with Cushing syndrome has been reported.
- Sporadic cases
  - Somatic KCNJ5 mutations (female predominance) found in 10–68% of sporadic APAs.
  - Somatic ATP1A1 and ATP2B3 mutations (male predominance), and CACNA1D mutations are also found in sporadic APA.
- APA may rarely be seen in multiple endocrine neoplasia type 1 (MEN-1).

COMMONLY ASSOCIATED CONDITIONS

Aldosterone excess may independently increase the risk of coronary artery disease, stroke, left ventricular hypertrophy, atrial fibrillation, heart failure, diabetes mellitus type 2, obstructive sleep apnea, renal disease, and bone loss.

Pregnancy Considerations

- Increases in aldosterone production and plasma renin activity (PRA) are physiologic during pregnancy; confirmation tests are not recommended.
- The diagnosis of PA during pregnancy relies on a repeatedly suppressed plasma renin level.
- Avoid **spironolactone** and ACE inhibitors.

DIAGNOSIS

HISTORY

- Usually asymptomatic.
- ROS: headaches, muscle weakness, fatigue, cramping, polyuria, polydipsia, paresthesias, or tetany (due to the hypokalemia).
- Family history of HTN (early onset, <40 years old).

PHYSICAL EXAM

- HTN, generally >150/100 mm Hg.
- Funduscopy: HTN retinopathy.
- Displaced apical pulse (ventricular hypertrophy).

DIFFERENTIAL DIAGNOSIS

- Diuretic use
- Essential HTN
- Renovascular HTN
- Pheochromocytoma
- Congenital adrenal hyperplasia
- Corticosteroid excess (exogenous or endogenous)
- Exogenous mineralocorticoid
- Bartter syndrome
- Licorice (glycyrrhizinic acid) ingestion

DIAGNOSTIC TESTS & INTERPRETATION

Initial Tests (lab, imaging)

- The Endocrine Society recommends screening in high prevalence groups, including (1)[C]:
  - Sustained HTN >150/100 mm Hg
  - Drug-resistant HTN (>140/90 mm Hg despite three anti-HTN drugs, including a diuretic)
  - Controlled HTN (<140/90 mm Hg on four or more anti-HTN drugs, including a diuretic)
  - HTN with hypokalemia (spontaneous or diuretic-induced)
  - HTN with adrenal incidentaloma
  - HTN with sleep apnea
  - HTN with family history of early-onset HTN or stroke at young age (<40 years)
  - Hypertensive first-degree relatives of PA patients
- Screening: aldosterone-to-renin ratio (ARR) (1)[C]
  - Step I: Is renin suppressed and aldosterone increased?
    - Liberalize Na^+ intake and correct hypokalemia (hypokalemia blunts aldosterone production).
    - Ideally, collect sample in the morning, after an initial 2-hour ambulatory period and 5 to 15 minutes in a seated position.
    - Ideally, withdraw agents that affect the ARR for at least 4 weeks (**spironolactone**, **eplerenone**, **amiloride**, **triamterene**, K^+ wasting diuretics, licorice products).
    - Measure plasma aldosterone concentration (PAC) and measure renin by testing for PRA or for direct renin concentration (DRC).
    - ARR cut off 20 to 40 when using PRA; most commonly used >30 (PAC in ng/dL and PRA in ng/mL/hr); PAC should be increased and PRA suppressed (>10 to 15 ng/dL and <1 ng/mL/hr, respectively).
    - ARR cut off 2.4 to 4.9 when using DRC (PAC in ng/dL and DRC in mU/L); estrogen-containing medications may lower DRC and cause false-positive ARR.
    - If ARR is not diagnostic and HTN can be controlled on relatively noninterfering medications (verapamil SR, **hydralazine**, **prazosin**, **doxazosin**, **terazosin**), withdraw other medications that may affect the ARR for at least 2 weeks: β-blockers, α_2 agonists, NSAIDs, ACE inhibitors, ARBs, renin inhibitors and dihydropyridine CCB.
    - If all potentially problematic agents cannot be safely withdrawn, the results considered in the light of the potential confounding factors.
    - If aldosterone receptor antagonists cannot be safely discontinued, testing can be pursued as long as renin is suppressed.

Follow-Up Tests & Special Considerations

- Patients with a positive ARR should have confirmatory testing.
- In the setting of spontaneous hypokalemia, suppressed PRA, plus PAC >20, there may be no need for further confirmatory testing (1)[C].
  - Step II: Is increased aldosterone production suppressible?
    - The current literature does not identify a gold standard confirmatory test.
    - Four confirmatory tests are available (1,2)[C].
      - *Oral sodium-loading test* (*OST*)
        - Increase Na^+ intake to >200 mmol/day (~6 g/day) for 3 days.
        - 24-hour urine aldosterone is measured from the morning of day 3 to the morning of day 4.
        - Elevated urinary aldosterone (>12 to 14 ng/24 hr) makes PA highly likely.
      - *Saline infusion test* (*SIT*)
        - Patients stay in the recumbent position for at least 1 hour before and during the infusion of 2 L of NS over 4 hours starting at 8:00 to 9:30 AM.
        - Renin, aldosterone, cortisol, and K^+ are drawn at time zero and after 4 hours.
        - Postinfusion PAC <5 ng/dL makes PA unlikely, 5 to 10 ng/dL indeterminate, and >10 ng/dL is a sign of a very probable PA.
        - Seated SIT (SSIT) testing may be more sensitive than recumbent SIT (RSIT), especially for posture-responsive forms; for SSIT, a postinfusion PAC of >6 ng/dL confirms PA (provided plasma cortisol is lower than the value obtained basally, to exclude a confounding ACTH effect).
        - Note: OST and SIT should not be performed in patients with severe uncontrolled HTN, renal insufficiency, cardiac insufficiency, cardiac arrhythmia, or severe hypokalemia.
      - *Fludrocortisone suppression test* (*FST*)
        - Patients receive **fludrocortisone** 0.1 mg q6h for 4 days, together with KCL (to maintain plasma K^+ close to 4.0 mmol/L).
        - NaCl 30 mmol TID and unrestricted salt intake to maintain a urinary Na^+ excretion rate of at least 3 mmol/kg body weight.
        - On day 4, PAC and PRA are measured at 10 AM with patient seated; cortisol is drawn at 7 and 10 AM.
        - PAC >6 ng/dL confirms PA (provided PRA is <1 ng/mL/hr and plasma cortisol

is lower than the value at 7 AM, to exclude a confounding ACTH effect).
    - *Captopril challenge test*
        - Patients receive **captopril** 25 to 50 mg PO after sitting or standing for at least 1 hour.
        - Measure PRA, PAC, and cortisol at time zero and 1 to 2 hours after; patient remains seated during the entire test.
        - Aldosterone is normally suppressed by **captopril** (>30%); in patients with PA, PAC remains elevated and PRA remains suppressed.
- Step III: Confirmed cases should undergo an adrenal CT scan to exclude ACC (1)[C].
    - High-resolution CT scan with thin sections (2 to 3 mm) is preferred over MRI; MRI has no advantage over CT, it is more expensive, and has less spatial resolution (1)[C].

Diagnostic Procedures/Other

- Subtype differentiation is important for determining treatment options.
- Adrenal venous sampling (AVS) has emerged as the reference standard to distinguish unilateral from bilateral excess aldosterone production in patients with established PA (1,3)[C].
- In patients <35 years with marked PA and unilateral adenoma on CT, AVS may not be needed before surgery (1)[C].
- AVS should not be performed in patients at unacceptable high-surgical risk, or not desiring surgery, or with suspicion for ACC, or with proven/suspicious for FH syndromes (1,3)[C].
- AVS requires experienced multidisciplinary team with a standardized protocol (1,3)[C].
- In experienced centers, AVS has a low complication rate (<2.5%) (1,3)[C].
- AVS success rate may be improved by pre/intraprocedural synthetic ACTH administration and rapid intraprocedural measurement of cortisol (4)[C].

TREATMENT

- Treat HTN and electrolyte abnormalities, particularly hypokalemia, if present.
- Surgery is the definitive treatment for unilateral disease (5)[A].
- Medical management with aldosterone antagonists is the treatment of choice for bilateral hyperplasia; may be an alternative for patient not interested in surgery or poor surgical candidates (5)[A].
- For FH type I/GRA: Prefer long-acting glucocorticoids at the lowest effective dose (**dexamethasone** 0.25 to 0.50 mg/day or **prednisone** 2 to 3 mg/day) to normalize blood pressure (BP) and K^+ to aldosterone antagonists.

MEDICATION

First Line

- Mineralocorticoid receptor antagonist (MRA): **spironolactone**, or **eplerenone** as an alternative (1)[C]; monitor K^+ and creatinine frequently during the first 4 to 6 weeks of treatment.
- **Spironolactone**: Initial dose of 12.5 to 25.0 mg/day and titrate up to 400 mg/day as needed to achieve normokalemia without K^+ supplements (1)[C].
- **Eplerenone**: The starting dose of **eplerenone** (has 50% potency of **spironolactone**) is 25 mg twice daily; the maximum dose approved by the FDA for HTN is 100 mg daily due to risk of hyperkalemia; however, this is not a concern in patients with PA.
- To effectively treat PA, higher doses are frequently required, targeting unsuppressed renin.
- Patients on subtherapeutic doses of MRA (i.e., renin remains suppressed) have increased risk of CV events and mortality (6)[B].

Second Line

- Other K^+ sparing diuretics: **amiloride**, **triamterene.**
- Antihypertensive agents: CCB, ACE inhibitor, ARB, β-blocker, or low-dose thiazide diuretic.
- Contraindications: K^+ sparing agent and ACE inhibitors in renal failure, hyperkalemia, pregnancy.
- Precautions: Monitor serum K^+ and creatinine closely after any adjustment in K^+ replacement or K^+ sparing agent (monitor closely for 4 to 6 weeks).

ISSUES FOR REFERRAL

- Experienced interventional radiologist for AVS.
- Surgery for unilateral laparoscopic or robotic adrenalectomy in unilateral APA or hyperplasia.

SURGERY/OTHER PROCEDURES

Surgical resection (laparoscopic or robotic adrenalectomy) is the treatment of choice for unilateral disease (APA or hyperplasia) (1)[C],(5)[A].

ADMISSION, INPATIENT, AND NURSING CONSIDERATIONS

- Refractory HTN, hypertensive urgency/emergency
- Severe hypokalemia
- Cardiovascular events
- Careful monitoring of BP and telemetry for arrhythmia
- Discharge when normokalemic and stable BP

ONGOING CARE

FOLLOW-UP RECOMMENDATIONS

- K^+ supplements, anti-HTN therapy, and **spironolactone** may need to be stopped/decreased after surgery.
- High Na^+ diet may be needed to avoid the hyperkalemia that can develop due to chronic contralateral adrenal gland suppression during the first few weeks postop.
- BP levels return to normal in about 50% of patients after unilateral adrenalectomy for APA.

Patient Monitoring

- Check BP and serum K^+.
- PAC and PRA/DRC should be checked early after surgery to assess biochemical response and to monitor MRA efficacy.

DIET

Low Na+, high K+

PATIENT EDUCATION

- HTN management
- Medication management
- Diet

PROGNOSIS

- Earlier intervention is linked with decreased risk of cardiovascular and renal disease; treatment is linked with halting or reversal of end-organ damage.
- BP is reduced in nearly all treated patients.
- Treatment may result in decreased glomerular filtration rate; this should not be a reason to avoid treatment (hyperfiltration due to aldosteronism can lead to underestimation of renal disease at baseline).
- Chronic therapy with **spironolactone** can be limited by gynecomastia, decreased libido, and impotence in men; menstrual abnormalities in women (consider **eplerenone** in these cases).
- To better predict resolution of HTN after adrenalectomy, use the Aldosteronoma Resolution Score (ARS):
    - BMI <25 kg/m^2 (1 point)
    - Female sex (1 point)
    - Duration of preop HTN <6 years (1 point)
    - <2 preop anti-HTN medications (2 points)
- 27.6% of ARS of 0 to 1 had cure of HTN, whereas 75% of ARS 4 to 5 had complete resolution of HTN; this scoring system does not account for hypokalemia.
- Treatment of PA results in substantial improvement of quality of life (QoL); QoL improves more after adrenalectomy than after initiation of medical therapy.

COMPLICATIONS

- Increased CV events in untreated PA compared to patients with essential HTN.
- Increased CV events and mortality if treated with subtherapeutic doses of MRA (6)[B].

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CODES

ICD10

- E26.09 Other primary hyperaldosteronism
- E26.01 Conn's syndrome

CLINICAL PEARLS

- PA screening is recommended in high-risk patients.
- Calculate ARR in patients at increased risk.
- Confirmed cases should undergo high-resolution CT scan to exclude ACC.
- If surgery is desired and patient is not a poor surgical candidate, AVS should be performed to exclude BIH.
- Unilateral adrenalectomy is the treatment of choice for unilateral APA or hyperplasia.
- MRAs are the treatment of choice for BIH.
- Titrate MRA dosage to unsuppressed PRA.